Cornell University

Graduate School of Medical Sciences 1987 • 1988

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Academic Calendar 1987–88

1987

Registration for Quarter I* and Fall semester**; orientation for new students	Tuesday and Wednesday, September 1 and 2
Quarter I and Fall semester begin	Thursday, September 3
Labor Day Holiday	Monday, September 7
Quarter I ends	Wednesday, October 28
Examinations for Quarter I	Wednesday, November 4–Friday, November 6
Registration for Quarter II*	Friday, November 6 and Monday, November 9
Quarter II begins	Monday, November 9
Thanksgiving recess	Thursday and Friday, November 26 and 27
Winter recess: Instruction suspended 5:00 p.m.	Friday, December 18

1988

Winter recess: Instruction resumed 9:00 a.m.	Monday, January 4
Last day for completing requirements for January degrees	Friday, January 15
Martin Luther King, Jr.'s Birthday observed	Monday, January 18
Quarter II and Fall semester end	Tuesday, January 19
Conferral of January degrees	Wednesday, January 20
Examinations for Quarter II	Tuesday, January 26–Friday, January 29
Registration for Quarter III* and Spring semester***	Friday, January 29 and Monday, February 1
Quarter III and Spring semester begin	Monday, February 1
Washington's Birthday observed	Monday, February 15
Quarter III ends	Monday, March 28
Examinations for Quarter III	Monday, April 4–Thursday, April 7
Spring recess	Friday, April 8–Tuesday, April 12
Registration for Quarter IV	Tuesday, April 12 and Wednesday, April 13

Quarter IV begins	Wednesday, April 13
Eighth Annual Vincent duVigneaud Memorial Research Symposium; no classes	Tuesday, May 3
Last day for completing requirements for May degrees	Thursday, May 12
Commencement Day, conferral of May degrees	Tuesday, May 24
Memorial Day Holiday observed	Monday, May 30
Quarter IV and Spring semester end	Wednesday, June 8
Examinations for Quarter IV	Tuesday, June 14–Friday, June 17

Summer Term 1988

Registration for summer research	Monday, June 27
Summer research term begins	Monday, June 27
Summer research term ends	Friday, August 19
Last day for completing requirements for August degrees	Friday, August 19
Conferral of August degrees	Wednesday, August 24

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*for students enrolling in courses

**for students conducting research only, who are on leave of absence, or are in absentia.

***for students changing from course work to research, who are going on leave of absence, or who are converting to in absentia status.

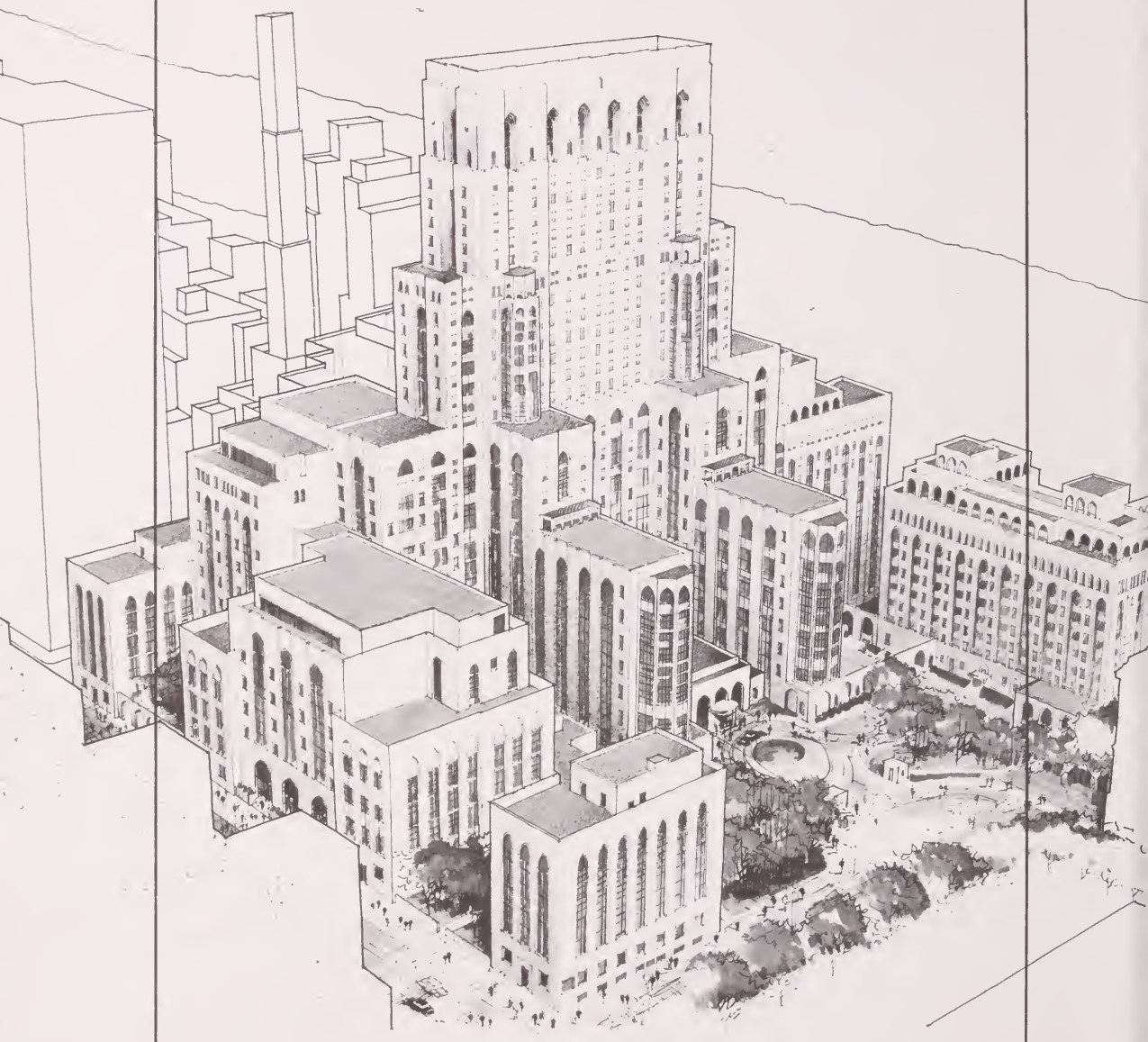
Note: Courses are taught on a quarterly basis; degrees are granted at ends of the Fall and Spring semesters and of the summer term. The dates shown in the calendar are subject to change at any time by official action of Cornell University.

In enacting this calendar, the Graduate School of Medical Sciences has scheduled classes on religious holidays. It is the intent of the school that students missing classes due to the observance of religious holidays be given ample opportunity to make up work.

Contents

The courses and curricula described in this Catalog, and the teaching personnel listed herein, are as of July 1, 1987 and are subject to change at any time by official action of Cornell University.

Cornell Medical Center



Cornell University
Graduate School of Medical Sciences

Purpose

The Graduate School of Medical Sciences, a semi-autonomous component of the Graduate School of Cornell University, provides opportunities for advanced study and research training in specific areas of the biomedical sciences. Graduate programs leading to the degrees of Doctor of Philosophy are offered in biochemistry, cell biology and genetics, immunology, molecular biology, neurobiology and behavior, pharmacology, and in physiology and biophysics. Certain of these fields of study also offer programs leading to the degree of Master of Science. Collaborative programs with Cornell University Medical College lead to the combined degrees of Doctor of Philosophy and Doctor of Medicine.

The faculty of the Graduate School of Medical Sciences recommends the award of advanced general degrees not only as the result of the fulfillment of certain formal academic requirements, but also as evidence of the development and possession of a critical and creative ability in science. Demonstration of this ability is embodied in a dissertation which the candidate presents to the faculty as an original research contribution in the chosen area of study.

A close working relationship between student and faculty is essential to the program of the Cornell University Graduate School of Medical Sciences. Guidance for each student is provided by a Special Committee, a group of at least three faculty members selected by the student. This Special Committee is granted extraordinary independence in working with its student. Other than a broad framework of Graduate School of Medical Sciences requirements for residence, examinations, and a thesis, and additional requirements of the particular field of study chosen by the student, the Special Committee is free to design an individualized program of study with its students. No overall course, credit-hour, or grade requirements are set by the Graduate School of Medical Sciences. A student is recommended for a degree whenever the Special Committee judges the student qualified.

History

The opportunity for graduate study leading to advanced general degrees in the biomedical sciences was first offered at the Cornell University Medical College, in cooperation with the Graduate School of Cornell University, in 1912. In June of 1950, Cornell University, in association with the Sloan-Kettering Institute for Cancer Research, established additional opportunities for graduate study by forming the Sloan-Kettering Division of the Medical College. The resulting expansion of both graduate faculty and research training opportunities on the New York City Campus prompted the organization in January 1952 of the Graduate School of Medical Sciences, composed of two cooperative but separate divisions, known as the Medical College Division and the Sloan-Kettering Division. The Graduate School of Medical Sciences was given full responsibility for advanced general degrees granted for study in residence on the New York City campus of Cornell University.

Facilities

Despite the divisional structure of the Graduate School of Medical Sciences, the general facilities of the Divisions such as libraries, dining facilities, and recreational resources are open to all students.

The Medical College Division. The buildings along York Avenue between 68th and 70th Streets accommodate both Cornell University Medical College and the Medical College Division of the Graduate School of Medical Sciences. Facilities available to graduate students include the Samuel J. Wood Library with a collection of over 136,000 volumes and subscriptions to 2,100 current journals, lecture rooms, teaching laboratories, seminar rooms and libraries of the basic science departments. Extensive research facilities are provided for faculty and students.

The Sloan-Kettering Division. Its facilities are located within the Sloan-Kettering Institute for Cancer Research, which consists of the Howard, Kettering, and Schwartz Laboratory buildings on East 68th Street. In addition, the Walker Laboratory is located in Rye, New York. Each provides lecture and seminar rooms, and together represent more than 100 laboratories, which are available for biomedical research training. The Medical Library, Nathan Cummings Center with 27,100 volumes of books and journals is located near the 68th Street complex.

Organization

The faculty of the Graduate School of Medical Sciences is composed of the faculties of the Medical College Division, consisting primarily of the professional staff of the basic science departments of Cornell University Medical College, and of the Sloan-Kettering Division, consisting of those professional staff members of the Sloan-Kettering Institute for Cancer Research who hold faculty appointments.

Graduate training is offered in several areas of the biomedical sciences. These Programs of Study include faculty members from the two Divisions who have related research and teaching interests.

Executive Committee

The Executive Committee is both the administrative and judicial board of the Graduate School of Medical Sciences and its members have continuing responsibility for the academic affairs of the school. The Committee is composed of the Chairpersons of the graduate programs, the Dean and Associate Dean, the Provost for Medical Affairs of Cornell University, the Director of the Sloan-Kettering Division, the Chairperson and Vice-Chairperson of the Faculty Advisory Committee (see below), and two non-voting, elected student representatives.

The Executive Committee considers such matters involving the interests and policies of the Graduate School of Medical Sciences as are referred to it by the Faculty Advisory Committee, by individual members of the Faculty, or are generated upon its own initiative. The Committee approves the addition or deletion of fields of study, reviews the admission of students, approves a student's major and minor fields, reviews the curriculum and requirements for degrees.

The Executive Committee is chaired by the Dean, who is the academic administrative officer of the Graduate School of Medical Sciences and is also an Associate Dean of the Graduate School of Cornell University. The Associate Dean, who is also an Assistant Dean of the Graduate School of Cornell University, is the Secretary of the Executive Committee.

Faculty Advisory Committee

The Faculty Advisory Committee is the primary body representing the views of the Faculty of the Graduate School of Medical Sciences. The Committee advises the Dean and the Executive Committee on the impact of educational and policy matters under their consideration and recommends changes in educational activities, procedures, and policy of the Graduate School of Medical Sciences.

The Faculty Advisory Committee is composed of elected faculty representatives from the graduate programs and one elected student representative from each Division. The Chairperson and Vice-Chairperson of the Committee are elected by its membership. Non-voting members are the Dean and Associate Dean, the Provost for Medical Affairs of Cornell University, and the Director of the Sloan-Kettering Division.

Special Programs

Medical Scientist Training Programs (M.D.-Ph.D.)

These programs are designed to expose a student to both medical and graduate disciplines during a six-year course of study. The combination of skills in basic research and experience in a clinical setting will prepare graduates from this program to pursue investigative careers in the biomedical sciences or in clinical medicine. The student spends the first two years as a medical student studying the basic medical sciences and attending regular graduate seminars. The summer months are spent in the laboratory learning experimental techniques and doing research. The third, fourth, and fifth years of the student's program are spent as a full-time graduate student and are devoted mainly to laboratory research and writing the thesis. The sixth year of the program is devoted to clinical clerkships. This six-year program represents the minimum time required to satisfy residence requirements of both the M.D. and Ph.D. degrees at Cornell University. Successful applicants to the program will become M.D.-Ph.D. Fellows and will receive a full tuition scholarship and a stipend covering living expenses for the six-year period.

Separate Medical Scientist Training Programs are offered by the Medical College and Sloan-Kettering Divisions:

M.D.-Ph.D. Program at the Medical College Division: Preclinical and clinical training are provided by the faculty of Cornell University Medical College, while graduate education in research is offered by the faculty of the Medical College Division of the Cornell University Graduate School of Medical Sciences.

M.D.-Ph.D. Program at the Sloan-Kettering Division: This program is sponsored collectively by the Sloan-Kettering Division and Cornell University Medical College. The program requirements include the research-based Sloan-Kettering Division Ph.D. curriculum and the Cornell University Medical College curriculum.

For application to these programs, see p. 57.

Ph.D.-M.D. Program

Students enrolled in the Graduate School of Medical Sciences may be eligible for admission into the Ph.D.-M.D. Program, jointly sponsored by the Medical College and the Graduate School of Medical Sciences. This program is designed for those graduate students who find that their teaching and research goals require the acquisition of the M.D. degree in addition to the Ph.D. degree. The program is *not* designed as an alternate path for students who have the M.D. degree as their primary goal, but who have not been accepted by a medical school. Those who know, at the time of application to Cornell, that they want to pursue a course of study leading to both degrees should apply to one of the M.D.-Ph.D. programs described above.

See p. 57 for application and graduation requirements of the Ph.D.-M.D. program.

Faculty and Research Activities

Biochemistry

Faculty

John P. Blass
Adele I. Boskey
Esther M. Breslow
Arthur J. L. Cooper
Gordon E. Fairclough
Jerald D. Gass
Jack Goldstein
Owen W. Griffith
David P. Hajjar
Rudy H. Haschemeyer
Bernard L. Horecker
Chun-Yen Lai
Raymond E. Lockard
Alton Meister
Ursula Muller-Eberhard
Abraham Novogrodsky
Julian R. Rachele (Emeritus)
Albert L. Rubin
Edward T. Schubert
Richard I. Soffer
Kurt H. Stenzel
Suresh S. Tate
Sidney Udenfriend
Daniel Wellner
Kenneth R. Woods
David Zakim

Research Activities

Members of the Biochemistry program are engaged in research spanning a wide spectrum of scientific areas. Thus, the research in *Dr. Meister*'s laboratory is concerned with the study of enzymes, especially those involved in amino acid, peptide, and protein metabolism. It involves the isolation of enzymes, the determination of their structure and properties, and the use of techniques such as isolation of mRNA and cDNA. The research is basic in nature, but significant relationships between this research and human disease have been discovered and are also being explored. Current work involves the metabolism and function of glutathione, including the relationships of this tripeptide to transport, metabolism, radiation, and chemotherapy.

Dr. Boskey's research is concerned with elucidating the factors controlling physiologic and dystrophic calcification. Hydroxyapatite formation and growth are studied in solution, in collagen gels in animal tissues and in cell culture. Recent studies have concentrated on the mechanism of action of proteoglycans (a mineralization inhibitor) and acidic phospholipids (promoters of mineralization). Studies are also in progress on: the role of vitamin D metabolites in bone lipid metabolism, the actions of matrix proteins in the regulation of calcification, and the effect of trace elements on bone metabolism.

Dr. Breslow is concerned with understanding the forces that determine the specificity of protein-protein interactions and the relationship between protein structure and function. She has been studying the interactions of the pituitary peptide hormones, oxytocin and vasopressin, with their storage protein, neurophysin. These studies are directed towards elucidating the binding site regions of the hormones and of the protein and at quantitating the energies of different components of the interaction. A second area of research concerns the mechanism by which proteins are degraded intracellularly during normal protein turnover. The aims of these studies are

Views of Manhattan from Cornell Medical Center.

to understand the precise role of ubiquitin, a small protein known to be involved in this process, and to elucidate the mechanisms underlying the selection of proteins for degradation.

Dr. Cooper's laboratory is working in the area of α-keto acid biochemistry and pyridoxal phosphate enzymes. Another area of active research is the metabolism of amino acids and ammonia in the brain. For this purpose, molecules labeled with short-lived radioisotopes are synthesized and their distribution in brain is analyzed by positron emission tomography. Cerebral energy metabolism, with particular emphasis on the malate-aspartate shuttle, and its disruption in various disease states are also being investigated.

Dr. Goldstein is studying the structure and function and erythrocyte surface antigens and is working on enzymatic methods for the removal of immuno-dominant sugars responsible for blood group A and B activity. He is also isolating and characterizing proteins exhibiting Rh structures, clarification of the genetic systems involved in Rh expression and modification of such antigenic sites by chemical and enzymatic procedures.

Dr. Griffith's research involves the design, synthesis and utilization *in vivo* of enzyme-selective inhibitors and substrates. These compounds are used both to evaluate and to control the metabolite flux through various pathways in intact animals. Recent studies have focused on the manipulation of glutathione and cysteine metabolism. Enzyme-selective inhibitors were developed that allow both glutathione biosynthesis and utilization to be blocked; techniques allowing extracellular cystine formation to be controlled were also developed. The inhibitors were shown to be useful in treating animal trypanosomiasis, enhancing oxidative killing of tumor cells, and preventing the formation of leukotriene C. New inhibitors are now being developed to allow *in vivo* control of carnitine metabolism. Applications of these compounds include the investigation and therapy of inherited diseases of lipid metabolism and diabetes.

Studies are currently in progress in *Dr. Hajjar*'s laboratory to investigate the interaction of endothelial cells which line blood vessels with the underlying smooth muscle cells in an attempt to define the role of the endothelium in the process of cholesterol accumulation during arteriosclerosis. In addition, the role of herpes viruses as an etiological agent in the pathogenesis of lipid accumulation and artheriosclerosis is under investigation by studying the virus' effects on intracellular cholesterol metabolism and lipoprotein binding and metabolism.

Research in *Dr. Haschemeyer*'s laboratory concentrates on the development of physical methods to study molecular structure and interactions. Current emphasis is directed toward computer modeling of biological flow methods and heterogeneous-phase reactions. Additional computer applications are directed toward defining prognostic factors and treatment protocols that optimize graft survival in kidney transplant patients.

Dr. Horecker is working on the isolation and characterization of peptides from the thymus gland and evaluation of their possible function as hormones that regulate cellular immunity. The cloning of the genes for prothymosin α and for parathymosin is a major current objective. Studies are also in progress on the properties of these substances as regulators of cellular immunity.

Dr. Lai's research is concerned with the structure and function of biologically active proteins. Work from his laboratory has shown that subunit A1 of cholera toxin is fully responsible for the toxin's ability to stimulate adenylate cyclase in mammalian cells. Isolated subunit A1 was also shown to catalyze an efficient transfer of the ADP-

ribose moiety from NAD to a membrane protein. Structural studies revealed the presence of a characteristic conformation for the NAD-binding site in the A1 subunit. In another project, evidence has been obtained for a two-domain structure of the angiotensin converting enzyme: the hydrophobic carboxy-terminal portion of the enzyme is anchored to the cell membrane and the amino-terminal half, with the active site, is exposed to the blood circulation. Structural analyses indicate that the lung and testis enzymes may be the products of two distinct genes, and experiments are in progress to explain the close similarities between the two enzymes.

Dr. Lockard's research group is investigating how proteins associate with mammalian messenger RNA (mRNA) molecules, and what the effect of these interactions are on mRNA function and stability. As model systems they are deriving complete secondary structures for both mouse α and β-globin mRNA using biochemical structure data, and phylogenetic and computer analysis. They have determined unique classes of proteins associated with the globin mRNA's by photo-induced cross-linking. Both the identity and site of attachment of these proteins being investigated with respect to the secondary structure models in order to generate a view of the architecture of the mRNAs in both the ribosome-free and translationally active states. They are probing the secondary structure of 18S ribosomal RNA in the small ribosomal subunit from rabbit reticulocytes and are interested in the relationship between ribosomal RNA structure and ribosomal proteins with mRNA. The unraveling of the multiple RNA:RNA and RNA:protein interactions occurring during translation should reveal important mechanisms of translational control of gene expression.

Dr. Muller-Eberhard is investigating the mechanisms of transport or iron protoporphyrin IX and its metabolic precursors by proteins in the blood stream as well as within hepatocytes. She is studying the exchange of porphyrins between proteins purified from serum and from hepatocytes; developing methods which delineate the function of these proteins in the delivery of porphyrins to hepatocytes and their intracellular distribution; and assessing the interaction of these proteins with artificial and biological membranes to learn how they may facilitate ligand transport across cellular and intracellular barriers.

The main objective of *Dr. Soffer*'s research is to characterize the physical, chemical, and biochemical properties of angiotensin II receptor which has been purified to a nearly homogeneous state from rabbit hepatic membranes.

Dr. Stenzel and Dr. Novogrodsky are interested in determining mechanisms involved in the regression of metastatic kidney tumor mediated by autologous killer cells activated by the oxidizing mitogens and recombinant interleukin 2 (rIL2). They are using *in vitro* systems to determine mechanisms of cell mediated cytotoxicity. These investigations include an analysis of mononuclear cell sub-populations involved, mechanisms of target cell lysis (membrane structures vs soluble factors), target specificity and synergistic effects of additional biologic response modifiers. *In vivo* systems are used to determine mechanisms of tumor lysis *in vivo* mediated by administration of activated killer cells and rIL2 in mouse tumor models. Clinical studies are underway in patients with metastatic renal cell carcinoma to determine efficacy and toxicity of adoptive immunotherapy. Alterations in patients' immune responses are determined. These studies include a structural and functional analysis of circulating mononuclear cell populations.

Dr. Tate is investigating the mechanisms by which the kidney epithelial cell achieves its structural and functional polarity. Two brush border membrane peptidases and a basolateral membrane enzyme, Na, K-ATP-ase, are being employed as

model systems to study the way in which these membrane proteins are synthesized, processed, sorted out and targeted to their final cellular locations using techniques of classical protein chemistry, immunology, cellular and molecular biology. Other research involves the isolation and characterization of enzymes responsible for the post-translational formation of modified N- and C-terminal residues of peptide hormones in the hypothalamus and pituitary.

Research in *Dr. Wellner*'s laboratory is concerned with the structure and function of enzymes involved in amino acid metabolism, such as L-amino acid oxidase and threonine deaminase. Techniques employed for the study of protein structure include amino acid analysis and microsequencing using a gas-phase protein sequencer. Amino acid analyses of urine and blood of patients with inherited and acquired defects in amino acid metabolism are carried out as part of an effort to improve the diagnosis and treatment of these diseases.

Recent Publications

Blass, J. P. (with Sheu, K. F. R., and Lai, J. C. K.), Properties and regional distribution of pyruvate dehydrogenase kinase in rat brain. J. Neurochem. 42:230–236, 1984.

Boskey, A. L. (with Weintroub, S.), The effect of vitamin D deficiency on rat bone lipid composition. Bone 7:277–281, 1986.

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Boskey, A. L. (with Raggio, C. L., and Boyan, B. D.), In vivo hydroxyapatite formation induced by lipids, J. Bone and Mineral Res. 1:409–415, 1986.

Breslow, E. The Use of Neurohypophyseal Hormone Analogs in the Study of Neurophysin-hormone interaction in *Handbook of Neurohypophyseal Hormone Analogs* (K. Jost, Ed.), CRC Press, 1987.

Breslow, E. (with Chandra, R. and Kappas, A.), Biochemical properties of the heme oxygenase inhibitors, Sn-protoporphyrin: Interactions with apomyoglobin and herum serum albumin, J. Biol. Chem. 261:3135–3141, 1986.

Breslow, E. (with Daniel, R., Ohba, R., and Tate, S.), Inhibition of ubiquitin-dependent proteolysis by non-ubiquitinatable proteins, J. Biol. Chem. 261:6530–6535, 1986.

Cooper, A. J. L. (with Lai, J. C. K.), Brain α-ketoglutarate dehydrogenase comples: kinetic properties, regional distribution and effects of inhibitors, J. Neurochem. 47:1376–1386, 1986.

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Cooper, A. J. L. (with Nieves, E., Coleman, A. E., File-DeRicco, S., and Gelbard, A. S.), Short-term metabolic fate of [^{13}N] ammonia in rat liver in vivo. J. Biol. Chem. 262:1073–1080, 1987.

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Hajjar, D. P. Herpesvirus infection prevents activation of cytoplasmic cholesteryl esterase in arterial smooth muscle cells. J. Biol. Chem. 261:7611–7614, 1986.

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Hajjar, D. P. (with Boyd, D. B., Harpel, P. C., and Nachman, R. L.), Histidine-rich glycoprotein inhibits the antiproliferative effect of heparin on smooth muscle cells. J. Exp. Med. 165:908–913, 1987.

Haschemeyer, R. (with Riggio, R. R., and Cheigh, J. S.), Transplantation in the elderly in *Geriatric Nephrology* (M. F. Michelis, B. B. Davis and H. G. Preuss, Eds.), Field, Rich Associates, Inc., New York, 1986, pp. 141–148.

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Lai, C. Y. (with Tyski, S., and Fujii, Y.) Active fragment of the insecticidal toxin from *B. thuringiensis,* Biochem. Biophys. Res. Commun. 141:106–111, 1986.

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Novogrodsky, A. (with Nordenberg, J., Wasserman, L., Beery, E., Aloni, D., Malik, H., and Stenzel, K. H.) Growth inhibition of murine melanoma cells by butyric acid and dimethylsulfoxide, Exp. Cell Res. 162:77, 1986.

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Stenzel, K. H. (with Nordenberg, J., Wasserman, L., Beery, E., Aloni, D., Malik, H., and Novogrodsky, A.) Growth inhibition of murine melanoma cells by butyric acid and dimethylsulfoxide. Exp. Cell Res. 162:77, 1986.

Stenzel, K. (with Wang, J., Suthanthiran, M., Walle, A., Lagman, M., Schwartz, R., Murthi, V., and Novogrodsky, A.) Anti-tumor properties of lymphocytes activated by the oxidizing mitogens. J. Immunol. 136:4735, 1986.

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Wellner, D. Separation of γ-glutamyl amino acids by ion exchange chromatography. Methods in Enzymol. 113:564–566, 1985.

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Cell Biology and Genetics

Faculty

Rosemary F. Bachvarova
David M. Bader
J. Michael Bedford
June L. Biedler
Anthony M. C. Brown
Raju S. K. Chaganti
Moses V. Chao
Zbigniew Darzynkiewicz
David B. Donner
Magdalena Eisinger
Donald A. Fischman
James L. German, III
Marvin Gershengorn
Patricia L. Jacobs
Eric A. Jaffe
Irwin Klein
Ione A. Kourides
Paul A. Marks
Malcolm A. S. Moore
Newton E. Morton
Ralph L. Nachman
Joel D. Pardee
Louis M. Pelus
James H. Ray
Richard A. Rifkind
Toby C. Rodman
Enrique Rodriguez-Boulan
Anuradha D. Saad
Marcello Siniscalco
Martin Sonenberg
Lisa Staiano-Coico
Paul Szabo
Martin Teintze
Paula Traktman
Doris A. Wall
David Zakim

Research Activities

The faculty of the Program in Cell Biology and Genetics conduct research in a broad range of fields which include the most exciting areas of genetics and cell, developmental and molecular biology. Specific interests include the developmental biology of

the early embryo and of muscle tissues; membrane biology; cell motility and the cytoskeleton; the molecular biology of cell growth, differentiation and oncogenic transformation; endocrinology and hormone receptors; human cyto-, population and somatic cell genetics; molecular virology. These studies are pursued using the most current cell biological, genetic, molecular and immunological methodologies in modern and well-equipped facilities.

The aim of *Dr. Bachvarova*'s research is to understand the control of gene expression during meiotic maturation and early development of mammalian embryos. Differential expression and processing of mRNA's in the developing oocyte and embryo, and the role of small cytoplasmic RNAs, are being investigated. *Dr. Bader*'s laboratory is concerned with the development of the heart. Specific interests are the differential expression of myosin heavy chains in the developing myocardium, and the mechanisms by which myocardial heterogeneity are generated. Monoclonal antibody and recombinant DNA technologies provide the basis for these studies of cardian myogenesis *in vivo* and *in vitro.* Processes in both the male and female reproductive systems which contribute to conception are the focus of research in *Dr. Bedford*'s laboratory. The cellular events undergone by spermatozoa during their maturation in the epididymis are under study; in the female, research is directed toward understanding sperm capacitation, sperm transport to the site of fertilization, and to the mechanism of fertilization.

Dr. Biedler's research concerns the genetic mechanisms underlying the cellular acquisition of resistance to cancer chemotherapeutic agents. Of current interest is the development of multidrug resistance, whereby cells selected with a single agent become cross-resistant to a wide variety of drugs. At least two amplified genes with a role in this process have been identified and are being studied. A second area of research is the cell biology of human neuroblastoma. This system, too, involves amplification of a specific gene and consequent cytogenetic abnormalities. Current studies are focused on the correlation of the differential expression of the N-myc oncogene and the EGF receptor gene with varying states of malignant transformation. *Dr. Brown* is studying the molecular mechanisms of oncogene action, concentrating on tumors induced by the mouse mammary tumor virus (MMTV). A major focus of his research is the function of the proto-oncogene *int*-1, which is activated by MMTV in mouse mammary tumors and is also implicated in early embryonic development. The major aim of *Dr. Chaganti*'s research is to define, using molecular, cytogenetic, and genetic epidemiologic methods, the role played by hereditary factors in the etiology of leukemia and cancer in humans.

Dr. Chao's research interests focus on gene expression and regulation in mammalian cells. Molecular genetic techniques are being applied to the gene for the nerve growth factor receptor and the role of the receptor in the mechanism of action of NGF and in the development of the nervous system. The development of cytochemical, biophysical, and molecular probes and techniques for the analysis of normal and tumor cells is the focus of *Dr. Darzynkiewicz*'s efforts. These probes may aid in cancer diagnosis, classification, and therapeutic evaluation. Mechanistic studies on the pharmacological action of DNA intercalating agents on tumor cells are also being undertaken. *Dr. Donner* is studying, on a molecular level, how peptide hormone-receptor interactions are regulated and translated into changes of cell growth, differentiation, or metabolism.

The identification and characterization of factors involved in growth stimulation or differentiation of skin melanocytes and keratinocytes *in vitro,* and the effect of

cells grown in tissue culture and growth factors on wound healing *in vivo,* is the focus of *Dr. Eisinger*'s work. *Dr. Fischman*'s research focuses on the cell and molecular biology of sarcomere assembly in developing skeletal and cardiac muscle. Monoclonal antibody and recombinant DNA technologies, as well as electron microscopy and fluorescence energy transfer, are being applied to the study of post-translation steps involved in myofibrillogenesis. Several aspects of human genetics are under study in *Dr. German*'s laboratory, including disturbances of malformation, disturbances of sexual development, and human cancer. Somatic cell genetic, cytogenetic, and molecular genetic approaches are being used.

The focus of *Dr. Gershengorn*'s laboratory is the understanding of hormonal regulation of cellular secretion. In particular, the stimulation of the anterior pituitary gland's secretion of thyroid-stimulating hormone and prolactin by thyrotropin-releasing hormone is under study. Research is now centered on the inositol lipid-calcium-protein kinase C pathway for signal transduction by TRH. *Dr. Jacob*'s laboratory is involved in cytogenetic and molecular analysis of human chromosome abnormalities, with emphasis on trisomies and sex chromosome abnormalities. *Dr. Jaffe*'s interest is in the response of endothelial cells to exogenous stimuli; current research includes study of the interaction of thrombin with endothelial cell surface proteins and the resultant induction of prostaglandin and thrombospondin production. Interactions of endothelial cells and white blood cells are also under study.

Dr. Klein is studying the effects of cardiac contractility and thyroid hormone on the regulation of cardiac myosin synthesis. Hormonal regulation of gene expression is the focus of *Dr. Kourides*' research. Of major interest to *Drs. Rifkind and Marks* are the cellular and molecular mechanisms that control coordinated gene expression and proliferation during induced cell differentiation. The principal experimental model is the murine erythroleukemia cell, which is a virally transformed red blood cell precursor arrested at a stage of the lineage called the colony-forming cell for erythropoiesis. Studies of the mechanisms implicated in the control of gene expression have demonstrated that the globin gene domains in murine erythroleukemia cells have acquired a unique molecular configuration with respect to DNA structure and chromatin configuration. Current studies are designed to identify and characterize regulatory elements in the globin gene domains that may be implicated in the process of induced gene expression, and to identify genes regulating cell proliferation including protooncogenes and related sequences.

Dr. Moore's primary interest concerns the concept of immune cell participation in hematopoiesis. The roles of prostaglandin E and T cells in normal hematopoietic and aplastic anemia, and in allogeneic marrow transplantation, are currently under investigation by *Dr. Pelus.* In this context, new techniques for treating mismatched marrow before transplantation are being developed. Together with Dr. Moore, Dr. Pelus is investigating the biological role of "pluripoietin" in sustaining long-term proliferation of pluripotential stem cells and primary myeloid leukemic cells. *Dr. Morton*'s laboratory is engaged in the study of genetic epidemiology, a science that deals with etiology, distribution, and control of disease in groups of relatives, and with inherited causes of disease in populations. Current emphasis is on origin of chromosomal aberrations, construction of genetic maps, and disease-marker associations.

The focus of work in *Dr. Nachman*'s laboratory is the biochemistry of platelet membranes and the macromolecular assembly of adhesive proteins on various cell surfaces and in the extracellular matrix. The structure and function of blood vessel walls is also under study. *Dr. Pardee*'s research is concerned with the regulation of the

actin cytoskeleton by actin-binding proteins. Regulatory proteins, such as myosin, severin and an actin filament bundling factor, have been isolated are being analyzed for their roles in cell migration, cell-substrate adhesion and neoplastic transformation. *Dr. Ray*'s research utilizes somatic cell genetics and molecular biology to analyze genomic instability in the chromosome-breakage syndromes, a group of genetically-determined human disorders that feature predisposition to the development of cancer.

Dr. Rodman's studies have, for a number of years, been concerned with the molecular organization of gamete chromosomes. A project currently under investigation deals with the postulated role of sperm-unique components in the pathogenesis of AIDS. *Dr. Rodriguez-Boulan*'s main interest is an understanding of the cellular and molecular mechanisms that regulate the traffic and targeting of membrane proteins in eucaryotic cells, with an emphasis on the polarized distribution of apical and basolateral plasma membrane proteins in epithelial cells. The experimental approaches utilized include cell and molecular biology, virology, immunology and electrophysiology. Biophysical analyses of thick filament assembly and myosin exchange in adult and embryonic skeletal muscle are the focus of *Dr. Saad*'s research effort.

The primary efforts in *Dr. Siniscalco*'s laboratory are the mapping of the human genome and its application to molecular diagnostics and the investigation of chromosomal fragility with special reference to aging and malignancy. The long-range objective of *Dr. Sonenberg* is the molecular description of membrane transduction of peptide hormonal messages after interaction with a specific membrane receptor or other membrane component. *Dr. Staiano-Coico*'s research involves the investigation of epidermal cell maturation and differentiation in culture in conjunction with preclinical and clinical studies on the usefulness of epidermal cell sheets as transplantable grafts. The use of flow cytometry in the detection of individuals at high risk for the development of colorectal cancer is also being examined.

Dr. Szabo's laboratory is investigating the molecular basis of cellular senscence, specifically concentrating on those genes which are normally expressed during the GO quiescent stage of the cell cycle but whose dysregulation may lead to senescence. Also under study is the molecular genetics of age-related disorders such as Alzheimer's disease in humans. At present, *Dr. Teintze*'s research if focused on two areas: the mechanism by which membrane proteins insert into the lipid bilayer, using model membrane systems, and the mechanism by which certain proteins are sorted to specific membranes within eukaryotic cells. The main focus of *Dr. Traktman*'s research is a molecular genetic analysis of vaccinia virus. Of particular interest are the temporal regulation of gene expression and the coordination of viral DNA replication. A variety of molecular, genetic and biochemical techniques are being employed to identify and characterize the viral genes and enzymes involved in DNA replication, homologous recombination, and the maintenance of DNA conformation.

Dr. Wall's laboratory conducts research in membrane biology, with an emphasis on receptor-mediated endocytosis and an analysis of intracellular membrane systems. The *Xenopus* oocyte is being used as a model cell to study the pathways of ligands and receptors during endocytosis, and the establishment and maintenance of distinct membrane systems during oogenesis and early embryonic development. The main interests of *Dr. Zakim*'s laboratory are interactions, within the plane of a membrane, between lipids and enzymes and between lipids and small hydrophobic substances. The major emphasis is on how the physical and chemical properties of the lipids regulate the function of integral membrane proteins.

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Immunology

Faculty

Anthony P. Albino
Edward A. Boyse
Yvon Cayre
Bo Dupont
Neal Flomenberg
Ulrich Hämmerling
Michael K. Hoffmann
Alan Houghton
Robert W. Knowles
Janet Lee
Kenneth O. Lloyd
Herbert F. Oettgen
Lloyd J. Old
Richard J. O'Reilly
Bijan Safai
Alan N. Houghton
Osias Stutman
Soo Young Yang

Research Activities

The main interests of the Immunology faculty are focused on the complex molecular and cellular mechanisms responsible for the development and regulation of the immune system. Research programs can be grouped into three main areas: 1) immunogenetics of cell surface molecules involved in the differentiation and function of normal and malignant lymphoid cells; 2) cellular immunology of the interactions between cells and their secreted products, and 3) tumor immunology of the transformed tumor cell and its host, aimed at designing possible diagnostic and therapeutic strategies. Research in all three areas involves studies using both animal models and human cells. Immunology is multidisciplinary in its approaches and has generated its own methodology (such as the production of monoclonal antibodies, and the continuous *in vitro* growth and cloning of lymphoid cells), in addition to using the methods of other disciplines, including biochemistry and molecular biology. For example, the analysis of the biological significance of a given lymphoid cell surface anti-

gen is not only studied using classical genetics and in functional assays using monoclonal antibodies, but also by isolating the molecule and defining its structure using biochemical techniques and characterizing its gene with the tools of molecular biology. Thus, the general approach of the research program is to define immunological events at the biological, biochemical and molecular levels.

In the field of tumor immunology, *Dr. Albino's* laboratory is examining the role of specific oncogenes in the pathogenesis of malignant melanoma. This includes a comprehensive study of the steps required for the transformation of human melanocytes and nevocytes. In addition, this laboratory also studies the structure and function of melanoma cell-surface differentiation proteins and their gene sequences.

Dr. Boyse's laboratory focuses on the description and understanding of genetic programs that specify the unique molecular constitution (surface phenotype) of the outer membrane of cells according to their developmental lineage and stage of differentiation.

The main research objective of *Dr. Cayre's* laboratory is to investigate the molecular basis of monocyte differentiation.

The central themes for *Dr. Dupont's* laboratory are the characterization of the genetic composition of the genes of the human major histocompatibility complex (MHC); the investigation of the molecular genetic basis for the expression of these extensive genetic polymorphisms of the MHC-encoded cell surface antigens as detected in the population; and the biological role of MHC gene products in immunoregulation and other biological functions. The laboratory is also involved in investigations in the area of transplantation immunology, particularly in relation to the understanding of mechanisms responsible for graft vs. host disease.

Investigations in *Dr. Flomenberg's* laboratory focus primarily on the activation and effector functions of human lymphocytes. A large portion of this work concerns the molecular interactions between the T cell and its target, focusing on the major histocompatibility complex gene products that initially activate or serve as targets for T cells, as well as the T cell surface molecules that are important for T cell function. Additional studies of autoreactive T cells, natural killer cells, and the molecular genetics of B cell differentiation are in progress.

For the mouse, the majority of genes encoding lymphocyte antigens are organized in distinct multigene families positioned on several chromosomes. Study of these gene clusters continues to be the major theme of *Dr. Hämmerling's* efforts. The immunogenetics of murine and human lymphoid and hemopoietic cell surface antigens using monoclonal antibodies is another area of Dr. Hämmerling's studies, with special emphasis on their role in T cell activation.

The main interest of *Dr. Hoffmann's* studies is the analysis of the direct and factor-mediated cellular interactions in the human and murine antibody responses *in vitro*.

Dr. Houghton's research program to investigate the pathogenesis and treatment of malignant melanoma arises from his interest in the biology of human solid tumors. Dr. Houghton views malignant melanoma as a paradigm for the pathogenesis of human cancer. His studies involve the phenotypic and genotypic expression of antigens related to differentiation and transformation of melanocytes.

The molecular genetics of the human major histocompatibility complex or HLA genes is the major area of study of *Dr. Lee's* laboratory. Her work currently concentrates on the molecular mechanisms regulating the expression of genes within the HLA region on human chromosome 6.

Investigations of the glycorproteins and glycolipids of human tumor cells and normal cells are the focus of research in *Dr. Lloyd's* laboratory. Particular emphasis has been placed on the biochemical identification and characterization of these components.

The main effort in *Dr. Oettgen's* laboratory is on the serological analysis of human cancer antigens, the human and cellular immune responses to human cancer, and the development and application of human cancer therapies using cancer antigens, immunogenic cancer vaccines and monoclonal antibodies.

Dr. Old's research is concerned with the development of two new approaches to cancer therapy: tumor necrosis factor (TNF) and monoclonal antibodies directed against surface determinants on malignant cells. The latter is part of a general effort to analyze the cell surface of human and murine tumors, with the aim to characterize the important surface molecules, mostly with monoclonal antibodies and other serological procedures.

The principal objective of *Dr. O'Reilly's* Bone Marrow Transplantation Program is the development and improvement of transplantation approaches for the treatment of lethal disorders of the blood system through an integrated program of clinical and basic research in immunology, hematology, genetics, and transplantation biology.

Investigation into the biology of epidermal keratinocytes and Langerhans cells is the focus of *Dr. Safai's* research, with the objectives of defining the antigenic components of the epidermal keratinocytes and their secretory capacity and characterizing lymphocyte-epidermal interactions.

The definition of the steps involved in the development, maintenance and function of T (thymus-dependent) cells through the use of murine models has been one of the main areas of *Dr. Stutman's* research. Another area of interest is the study of the immunological components of the tumor-host interaction. These studies include the definition of tumor-specific responses; examination of the role of such responses in affecting tumor development and behavior, and the production of specific and nonspecific cytotoxic cells that can kill tumor cells.

Dr. Yang is involved in studies of T-lymphocyte activation, lymphokine production and regulation, T-lymphocyte differentiation antigens and their functions, as well as the gene organization and regulation of gene expression in the Class I MHC genetic region in humans.

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Molecular Biology

Faculty

Francis Barany
Kenneth Berns
Peter Bësmer
Moses V. Chao
Eric Falck-Pedersen
Eli Gilboa
William S. Hayward
William Holloman
Jerard Hurwitz
Joseph Jack
Robert M. Krug
Elizabeth H. Lacy
Arthur Lustig
Kenneth J. Marians
Peter W. Melera
Norma Neff
Michael E. O'Donnell
Paul V. O'Donnell
Mary Ann Osley
Samuel Rabkin
Jeffery V. Ravetch
Ora M. Rosen
Ganes C. Sen
Michael B. Sheffery
David Solnick
Paula Traktman

Research Activities

Several of the Programs of the Graduate School of Medical Sciences jointly offer an interdisciplinary program of graduate research training in the structure, function and regulation of genetic elements; including control of normal gene expression, gene replacement, oncogenes and oncogene expression, oncogenic viruses, chromosome structure, nucleic acid replication, recombination and repair, mechanisms of cell determination, growth factors and their receptors and human gene therapy.

In the laboratories, the control of gene expression is studied in a variety of viral and cellular systems, in cell-free systems, in cell culture, and in the intact organism. Influenza virus and adenovirus serve as models for the control mechanisms involved in the synthesis, processing and translation of RNA, both in the cell and in cell-free systems. Various eukaryotic virus expression vectors are being constructed for these studies. The use of human retroviruses for human gene replacement therapy is also under development. Virus-infected cells are also being employed for molecular studies of interferon action. Cells responsive to specific inducing agents are used to elucidate the regulation of gene transcription by peptide hormones, by interferon, and by chromatin structure. The gene amplification or rearrangement events frequently observed in tumor cells reveal the profound effects of such DNA alterations on gene transcription. Mice carrying new genes introduced by injection of DNA into early embryos provide novel examples of tissue-specific control of gene expression.

Research of the mechanism of both prokaryotic and eukaryotic DNA replication employs cell-free replication systems. Model systems have been developed to study the replication of SV40, herpes-simplex, vaccinia and adenovirus as well as leading- and lagging-strand DNA synthesis on the bacterial chromosome. These studies aim to elucidate control elements and specific protein-nucleic acid interactions involved in DNA replication. Related studies are being carried out on the enzymological mechanisms involved in the recombination of chromosomes.

Much of the research on the control of cellular metabolism and growth focuses on crucial regulatory proteins involved in the transmission of signals at the cell membrane, including various cell surface receptors, protein kinases, and the calcium binding protein, calmodulin. In addition to biochemical and physiological studies, substantial effort is being made to isolate and determine the nucleotide sequences of the genes encoding these important proteins. How cell determination is affected by the alteration of the expression of specific genes in Drosophila is also under study.

The mechanism of action of viral and cellular genes directly implicated in neoplasia is under active investigation. The study of the mechanism of activation of these cellular genes and of their gene products to become oncogenes may provide insight into the molecular basis of human cancer.

Several laboratories focus on the cellular mechanisms that operate to control gene expression.

Dr. Krug's research focuses on the unique interaction of influenza virus with its host cells as a model system for elucidating control mechanisms involved in the synthesis, processing, and translation of both viral and cellular messenger RNAs.

Dr. Falck-Pedersen concentrates on developing an understanding of transcription in eukaryotic cells. In particular, a combined biochemical and molecular genetical approach is being used to analyze the termination of transcription by RNA polymerase II.

Both *Dr. Hurwitz*'s and *Dr. Solnick*'s laboratory are investigating the mechanisms of RNA splicing in eukaryotic cells. Whereas, Dr. Solnick studies the mechanisms operative during exon selection, Dr. Hurwitz studies the enzymes and enzymological processes involved. *Dr. Gilboa* is also characterizing the regulation of RNA processing in retroviruses.

Research in *Dr. Sheffery*'s laboratory is directed at understanding how proteins and DNA interact to form structures that influence gene transcription, using the mouse globin genes as a model. Particular effort is devoted to understanding tissue-specific gene expression.

Dr. Osley is investigating a similar phenomenon in yeast, studying the periodic expression of genes, such as those for histone, during the mitotic cell cycle in yeast.

Current work in *Dr. Neff*'s laboratory centers on the regulation of gene expression during the cell cycle of the simple eukaryotic baker's yeast, *Saccharomyces cerevisiae,* with calcium and calmodulin used as signal molecules during the cell cycle.

The program has a particularly strong concentration of faculty interested in the mechanisms and control of DNA replication and recombination in both eukaryotes and prokaryotes.

Dr. Hurwitz's laboratory uses the adeno and SV40 viral replication systems as probes for the enzymatic mechanisms of cellular DNA replication.

Both *Dr. Traktman*'s and *Dr. Rabkin*'s laboratory study the replication of large DNA viruses that encode their own DNA replication machinery. *Dr. Traktman* employs both biochemical and molecular genetical techniques to define the genes of vaccinia virus that are required for its replication. *Dr. Rabkin* is developing an *in vitro* system for the replication of herpes simplex viral DNA.

Using molecular genetics and biochemistry, the mechanisms that have evolved for replicating telomeres, the unique ends of chromosomes required for stability, and the role these sequences play in chromosome segregation are being investigated by *Dr. Lustig.*

The only families of linear DNA viruses that replicate in mammalian cell nuclei are the adeno-associated virus, the adenovirus and herpesvirus; the structure and function of one of these is the object study of *Dr. Berns*' laboratory. This virus was selected because it is thought to be highly amenable to detailed longitudinal investigation, since it readily establishes latent infections in continuous cell lines in culture derived from the normal host. A study of this virus may also have bearing on the molecular biology of cellular DNA replication and transcription.

DNA replication in prokaryotes is under study in the laboratories of *Dr. Marians* and *Dr. M. O'Donnell. Dr. Marians* focuses on studies of the enzymological mechanisms of DNA replication. The use of *in vitro* DNA replication systems composed of purified replication proteins enables detailed analyses of the interaction of the replication proteins with each other and with the DNA template. The role of topology in DNA replication, as well as the mechanisms of DNA topoisomerases, is also under study.

A detailed examination of the molecular mechanics of DNA replication is also the focus of *Dr. M. O'Donnell*'s laboratory. The dynamic motions on templates of the multi-protein replicative polymerase of *E. coli* and its interaction with other proteins at the replication fork are under study.

Another key cellular process that occurs on DNA is the exchange of genetic information through the process of recombination. *Dr. Holloman*'s laboratory studies the enzymological mechanisms involved in this complicated process. Model studies focus on the mechanism of synapsis and DNA strand exchange promoted by the rec 1 protein.

Several laboratories concentrate on the mechanism of control of cell growth, including mechanisms of neoplasia, response to hormone stimuli, mechanisms of cell determination, and human gene therapy.

Elucidation of the mechanism of action of insulin and related growth factors, leading to a detailed understanding of the receptor molecule as well as the mechanism(s) by which it transmits signals from the cell surface to its interior is the principal goal of *Dr. Rosen*'s research.

The gene for human nerve growth factor has been isolated by *Dr. Chao*'s laboratory. Recombinant DNA technology is being used to study the important structural features of the gene and the molecular basis of differential receptor expression during development.

In a series of experiments in *Dr. Ravetch*'s laboratory, the molecular genetic analysis of cell surface receptor proteins is being conducted, aimed at defining their modulation, mechanism of signal transduction and developmental regulation by isolation and characterization of genes that code for proteins binding immunoglobulin (FC receptors), by studying the interaction of the malaria producing parasite with the erythrocyte, and by characterizing the activated macrophage phenotype.

The production and analysis of embryonic lethal mutations and the identification of DNA sequences involved in regulating the stage-specific and tissue-specific expression of genes during mammalian development are the foci of *Dr. Lacy*'s research. The main experimental tool for these studies is the generation of transgenic mice. Among studies underway are those designed to identify sequences required for the specific expression of genes in T cells.

Dr. Jack's laboratory is involved in unraveling the molecular basis for changes in cell determination induced by mutations in the *cut* locus of Drosophila.

Current research objectives of *Dr. Besmer*'s laboratory are to investigate the structure and function of the proto-oncogene KIT to investigate its role in neoplastic transformation and to determine the basis of the differing neoplastic potential of the murine and feline *abl* viruses.

The creation of systems in the mouse for the study of the development of T-cell leukemia is the major focus of *Dr. P. O'Donnell*'s laboratory. Efforts are directed at characterizing the sequence of events in what now appears to be a multistep process of virus-induced transformation and progression to frank leukemia.

Dr. Hayward's research objective is to elucidate the mechanisms by which viral and non-viral agents induce neoplastic disease through the use of three classes of avian retroviruses as model systems.

Studies of the mechanisms of action of interferons against vesicular stomatitis virus, encephalomyocarditis virus, and retroviruses representing three virus groups with completely different replication strategies are underway in *Dr. Sen*'s laboratory.

Dr. Gilboa is developing retroviral vectors that can be used for human gene replacement therapy.

Dr. Melera's laboratory is involved in three major research projects: the first attempts to unravel the response of Chinese hamster lung cells (CHL) to antifolate challenge via the overproduction of two different molecular weight forms of the target enzyme dihydrofolate reductase; the second seeks to understand the role of gene amplification in the establishment of the multidrug-resistant phenotype displayed by CHL cells selected with vincristine; and the third is a study of DNA sequence amplification in human cancer, particularly neuroblastoma.

Dr. Barany uses the modern tools of the molecular biologist to engineer specific changes in proteins. Currently, the bacterial beta-lacatamase gene is being redesigned to produce an enzyme that has greater thermostability, lower susceptibility to inhibitors, and increased catalytic activity.

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Neurobiology and Behavior

Faculty

Harriet D. Baker
Ira B. Black
Dana C. Brooks
Arthur J. L. Cooper
Cheryl Dreyfus
Daniel Gardner
Michael S. Gazzaniga
James G. Gibbs, Jr.
Gary E. Gibson
Bernice Graftstein
Katherine A. Halmi
Lorraine Iacovitti
Tong H. Joh
Joseph E. LeDoux
David E. Levy
J. John Mann
Michiko Okamoto
Gavril W. Pasternak
Virginia M. Pickel
Fred Plum
Donald J. Reis
David A. Rottenberg
David A. Ruggiero
Leonard S. Schleifer
Jeri A. Sechzer
Gerard P. Smith
Peter E. Stokes
Gladys N. Teitelman
Jonathan Victor
Robert Young

Research Activities

Dr. Baker is interested in the factors underlying the determination and maintenance of neuronal phenotype. Using the olfactory system as a model, the research focus is on both catecholaminergic and peptidergic systems. Strain and species differences in neurotransmitter expression is another research interest. The techniques utilized in these studies include immunocytochemistry, neurochemistry and neuronal tracing techniques.

Dr. Black studies the molecular genetics underlying neuronal plasticity in the peripheral nervous system and the brain. A combination of *in vivo,* tissue culture, molecular biological, biochemical and morphologic techniques are employed to explore plasticity, and its role in the function of the nervous system. Developmental as well as aging models are being studied.

Dr. Brooks is using signal averaging techniques to study the manner in which auditory information is processed as it passes through the first relay nucleus of the auditory system in the cat. The potential fields generated by the subdivisions of this nuclear complex are being mapped using an IBM XT and computer graphics programs.

Dr. Cooper is working in the area of 2-keto acid biochemistry and pyridoxal phosphate enzymes. Another area of active research is the metabolism of amino acids and ammonia in the brain. For this purpose, molecules labeled with short-lived radioisotopes are synthesized and their distribution in brain is analyzed by positron emission tomography. Cerebral energy metabolism, with particular emphasis on the malate-asparate shuttle, and its disruption in various disease states is also being investigated.

Dr. Dreyfus' research examines phenotypic development of specific neurons of the central nervous system and emphasizes definition of environmental factors which may influence brain cell development. This work has concentrated on ontogeny of noradrenergic neurons of the locus coeruleus, as well as dopaminergic cells of the substantia nigra and peptidergic and cholinergic neurons of the striatum and nucleus basalis.

Dr. Gardner studies how neurons use chemical synaptic transmission to communicate with one another. Neurons in ganglia of the mollusc *Aplysia* are probed by intracellular recording, voltage clamping, patch clamping, and computer-based analysis to yield principles of organization of cell networks. One project focuses on properties of transmitter-activated channels which are altered postsynaptic currents. A second project combines neurophysiology with artificial intelligence techniques to ask how neuronal biophysics coordinates the activity of neurons in a network.

Dr. Gazzaniga utilizes neuropsychological approaches to behavior in man to examine the effects of corpus commissurotomy ("split-brain" surgery) on cognition with reference to interhemispheric interaction. These neuropsychological studies are carried out on patients who have had NMR (nuclear magnetic resonance) scans to determine the true extent of callosal separation.

Dr. Gibbs' research focuses on the neurobiology of motivated behaviors, especially the neuroendocrine mechanisms controlling feeding behavior in animals and the pathophysiology of eating disorders in humans.

Dr. Gibson examines the relation of calcium, oxidative metabolism and neurotransmitters to altered mental function and cell death. These interactions are examined in animal models of conditions that alter mental function in man (aging, hypoxia, and thiamin deficiency) as well as in tissues from Alzheimer patients. *In vivo* neurotransmitter metabolism is related to behavior and to molecular mechanisms *in vitro*. Human studies include enzyme measurements on autopsied brain as well as studies of lymphocytes, red blood cells and cultured skin fibroblasts.

Dr. Grafstein is concerned with problems of nerve regeneration and the response of nerve cells to injury. Techniques used include light and electron microscopy and radioactive isotope methods for analyzing the axonal transport of proteins and other cellular constituents.

Dr. Halmi's current research on anorexia nervosa and bulimia nervosa includes long term follow-up studies, investigation of appetite and satiety mechanisms in eating disorder patients, assessing taste preferences, neuroendocrine investigations and psychological assessments.

Dr. Iacovitti's research activities are directed towards the study of the developing nervous system. She is examining the principles which govern phenotypic expression of particular neurotransmitters in neurons of the peripheral and central nervous system.

Dr. Joh's main interests are the biochemistry and molecular genetics of neurotransmitter enzymes and receptors, and neurospecific protein. Multidisciplinary stud-

ies with molecular biologists, developmental biologists, and histochemists include the structural analyses of genes coding for neurotransmitter enzymes, gene regulation at the transcriptional level, quantitative analysis of mRNAs and gene expression during development and aging.

Dr. LeDoux studies the neural pathways mediating emotional information processing and memory. Classical conditioning techniques are used to endow sensory stimuli with emotional significance. Through the use of anatomical tracing, lesion, the electrophysiological recording techniques, the contribution of various brain areas and their fiber connections to the coding of stimulus meaning is analyzed.

Dr. Levy is developing techniques for predicting which comatose patients will recover and which will not. These efforts include utilization of positron emission tomographic scanning to study unconscious patients. He collects detailed clinical information on patients with stroke so that methods for predicting recovery from stroke can be developed as they have been for coma. Development of an easily-utilized data entry and analysis system designed to accept serial clinical data on patients with a variety of neurological illnesses is an integral part of these efforts. He is also investigating effects of tissue plasminogen activator (t-PA) in patients with acute stroke.

Dr. Mann's research focuses on aminergic receptor regulation and transmission abnormalities in the central nervous system and peripheral tissues. Human postmortem brain tissue, peripheral blood cells with beta adrenergic and serotonergic receptor complexes and related animal models are utilized to study the normal and diseased state. The laboratory has a particular interest in the neurochemical correlates of aggressive and anxiety disorders, suicidal behavior and the action of antidepressants.

Dr. Okamoto investigates pharmacologic and neuropharmacologic bases of the tolerance and dependence produced by general CNS depressants. Barbiturates, alcohol and benzodiazepines are the prototypes for the study. Synaptic dysfunctions in neonates born under the influence of these drugs will also be investigated.

Dr. Pasternak is studying the molecular pharmacology of centrally active analgesics. Work in the laboratory currently is focused upon the biochemical and pharmacological characterization of the various opiate receptor subtypes. One goal of the laboratory includes examining membrane-bound and affinity-purified receptors and their potential coupling with effector systems. Another is the correlation of the various subtypes with specific opiate actions *in vivo*. Finally, the anatomical localization of these sites within the central nervous system is studied with quantitative autoradiography. Many of these approaches have utilized a series of opiate affinity labels developed within the laboratory.

Dr. Pickel studies ultrastructural synaptic interactions between monoaminergic and peptidergic neurons in brain. Present research is directed toward a more complete understanding of the synaptic circuitry between neurons containing specific transmitters in the basal ganglia and in brainstem nuclei associated with central cardiovascular regulation. Specific interactions between central monoaminergic and peptidergic neurons are being examined in the adult and developing rat brain using immunocytochemical markers and electron microscopy. The peptides of current interest include opioids, substance P, neurotensin, and angiotensin.

Dr. Plum, Chairman of the Department of Neurology, focuses his research on cerebral metabolism in disease states and the identification of cellular-subcellular mechanisms responsible for ischemic cell death.

Dr. Reis' research interests are the central neural and neurochemical mechanisms governing control of the autonomic nervous system, cerebral blood flow and metabolism. His research also includes mechanisms governing the death of brain neurons in response to aging and injury.

Dr. Rottenberg's studies of cerebral blood flow and metabolism using positron emission tomography (PET) have focused on tissue pH, steroid-induced modifications of the blood-brain barrier and the metabolic pathology of the AIDS Dementia Complex. Ongoing studies are concerned with the metabolic correlates of higher integrative functions, including attention, and the functional anatomy of subcortical dementia.

Dr. Ruggiero's interests include: anatomical and neurochemical pathways in brain which maintain normal resting levels of arterial blood pressure; neural substrates of the baroreceptor reflex; pathways underlying the cerebellar regulation of autonomic activities and cerebral blood flow; areas of autonomic representation in cerebral cortex and brainstem reticular formation; adrenaline synthesizing neurons and their pathways in the central nervous system.

Dr. Sechzer's research interests include early development, behavioral toxicology, sensory receptors, and neural mechanisms of memory and learning, her current activities include: (1) The effect of lithium chloride on maternal behavior and early development; (2) Olfactory and gustatory thresholds in depression; (3) Bioethical issues concerning the use of animals in research education.

Dr. Smith is interested in the behavioral neuroscience of eating and its disorders. Current experiments include the measurement of central monoamines during eating behavior, the role of gut peptides, such as cholecystokinin, to stop eating, animal models of eating disorders using genetic and sham feeding rats, and the experimental analysis of taste and eating in human patients with various types of eating disorders.

Dr. Stokes studies neuroendocrine function in affective disease. Measurements of hypothalamic-pituitary-adrenocortical (HYPAC) function at various levels of this axis are obtained in patients with depression vs healthy normal controls and patients with other psychiatric diagnoses. Current specific interests include: response of the HYPAC system to administration of CRF, ACTH, dexamethasone and adrenocortical steroid blockers, pharmacokinetics of dexamethasone, measurement of multiple adrenal steroids, investigation of the relationship between HYPAC function and biogenic amine and sympathetic nervous system activity. A second area of interest is the investigation of lithium pharmacokinetics and the pharmacology-toxicology of lithium isotopes in animals and humans.

Dr. Teitelman's research interests include the cellular events controlling the expression of neurospecific proteins, such as neurotransmitter biosynthetic enzymes in autonomic ganglia of avian and mammalian embryos. Another area of her active research revolves around mechanisms involved in the differentiation of the endocrine cells of pancreatic islets from cells transiently expressing neurospecific enzymes. The techniques used in these studies include tissue culture, biochemistry and immunocytochemistry.

Dr. Young is interested in approaching relationships between brain neurotransmitter function and behaviors by studying major affective illness developing in late life. Indices of brain catecholaminergic function and behaviors are studied in individuals when symptomatic and after treatment. The laboratory measures applied include neurotransmitter metabolite excretion, neuroendocrine tests, brain imaging, and psychotropic drug concentrations.

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Pharmacology

Faculty

Joseph R. Bertino
Walter W. Y. Chan
Ting-Chao Chou
Diane F. Felsen
Owen W. Griffith
Charles E. Inturrisi
Roberto Levi
Mauricio Montal
Michiko Okamoto
Gavril W. Pasternak
Marcus M. Reidenberg
Arleen B. Rifkind
Francis M. Sirotnak
Hazel H. Szeto
Kyoichi A. Watanabe

Research Activities

The Graduate Pharmacology Program offers a broad spectrum of training opportunities from the molecular level to whole organism pharmacology.

Dr. Bertino is interested in the transfer of drug resistant genes into hematopoetic cells: Both electroporation and viral vectors have been studied as methods of introducing drug resistant genes (chloramphenicol-acetyl transferase; an altered dihydro-

folate reductase from 3T6 cells) into mammalian cells in culture, and into bone marrow cells. This method appears to be a powerful one for introducing substances into cells that are ordinarily excluded, and thus study their intracellular activity. The aim is to produce long-term expression of drug resistant genes in hematopoetic stem cells. Both *in vitro* (CFU_c) and *in vivo* (CFU_s) studies are being pursued in mice. The purpose of these studies is to produce drug resistance of marrow stem cells, thus allowing larger doses of the desired drug to be utilized for therapy.

Site specific mutagenesis of the dihydrofolate reductase gene: By using oligonucleotides with specific base changes, it has been possible to synthesize full-length cDNAs containing the desired mutation via the M-13 cloning system. The purpose of these studies is to better understand the effects of specific amino acid substitutions on substrate and inhibitor binding, and to hopefully develop an altered enzyme with a decreased affinity for methotrexate, but with good catalytic activity.

Development of a rapid *in vitro* test for detection of resistance to methotrexate and trimetrexate: Work has continued, utilizing leukemia cells from patients sensitive and resistant to methotrexate, to determine the degree and mechanism of drug resistance.

Studies with the new antifolate, trimetrexate: A phase 1 study has been completed. In rodent models, this drug was found to synergize with Carboxypeptidase G, a folate depleting enzyme, and when utilized following methotrexate treatment. Clinical studies are planned using these combinations.

Dr. Chan is interested in the functions and interactions of prostaglandins and neurohypophysial peptides in the kidney and the uterus. Current research covers investigative studies from subcellular levels to the whole organism. Certain analogs of oxytocin and vasopressin have been found to stimulate urinary sodium and water excretion. This renal effect of the peptide appears to be mediated by renal prostaglandin release. The biochemical mechanisms of this peptide-induced prostaglandin release is the principal concern of our research. Also studied are the renal activities of peptide analogs specifically synthesized for the project with the aim to discover specific prostaglandin-releasing peptides that may be useful for the treatment of renal hypertension.

In the uterus, the roles of prostaglandins and oxytocin in the regulation of uterine contractions and termination of pregnancy are investigated. This research seeks an understanding of the mechanism of initiation of labor, especially relating to preterm labor. Oxytocin-receptor and gap-junction formations in myometrial cells are important biochemical and morphological markers in the initiation of labor. Accordingly, a study is made of the effects of prostaglandins and oxytocin on the density of oxytocin-receptors and on the formation of gap-junctions in myometrial cells. Highly potent oxytocin antagonists have been synthesized for this project and their application in the prevention of preterm labor in the pregnant rat model will be investigated. Also studied are the physiological roles of ovarian oxytocin and uterine prostaglandins in the function of the corpus luteum, as well as the potential of intervention of this ovarian-utero axis in the regulation of fertility or as causal factor in abortion.

Dr. Chou's major research objectives are the study of: (1) the mechanisms of action of antitumor and antiviral agents; (2) the biochemical and pharmacological bases for the selectivity of effects on different targets; and (3) the derivation of theoretical formulations for dose-effect relationships that permits the automated computer analysis of relative potency and therapeutic index and facilitates the study of the interaction of multiple drugs in combination chemotherapy. The compounds of current in-

terest include potent antiherpes viral agents, anti-human immunodeficiency virus (anti-HIV) agents, classical antifolate analogs and lipid-soluble antifolates. Emphasized are pharmacodynamics, pharmacokinetics and preclinical toxicology, the determination of affinity and efficacy of drug interaction with enzymes or other targets, the elucidation of molecular events following the binding or incorporation of a drug into macromolecules, and the development of computer programs for drug evaluation, especially the synergism/antagonism of drugs in combinations. Currently several of the compounds mentioned above are in clinical trials. Also, software for dose-effect analysis has recently been developed for microcomputers.

Dr. Felsen is interested in the role of arachidonic acid metabolites (AAMs; prostaglandins, hydroxy acids and leukotrienes) and other mediators of inflammation (e.g., platelet-activating factor) in renal and hepatic function. The role of these compounds both *in vivo* and *in vitro* is studied using a combination of techniques. These include measurement of renal blood flow, both isotopically and nonisotopically, glomerular filtration rate and other parameters of renal function (Na^+ and K^+ excretion, water excretion, etc.). *In vitro,* both isolated organs and cell culture techniques are used for studies of renal and hepatic cells. These methods may provide an understanding of the molecular mechanisms involved in the interaction of AAMs and other inflammatory mediators in different models of renal and hepatic disease.

Dr. Griffith's research involves the design, synthesis and utilization *in vivo* of enzyme selective inhibitors and substrates. These compounds are used both to evaluate and to control the metabolite flux through various pathways in intact animals. Recent studies have focused on the manipulation of glutathione and cysteine metabolism. Enzyme-selective inhibitors were developed that allow both glutathione biosynthesis and utilization to be blocked; techniques allowing extracellular cystine formation to be controlled were also developed. The inhibitors were shown to be useful in treating animal trypanosomiasis, enhancing oxidative killing of tumor cells, and preventing the formation of leukotriene C. In other studies, novel carnitine analogs were synthesized as inhibitors of carnitine palmitoyltransferase and were shown to block long-chain fatty acid oxidation *in vivo.* In mice with diabetes, a disorder characterized by underutilization of glucose and overutilization of fats, these compounds prevent ketoacidosis and restore normal blood glucose levels. Studies are continuing in which carnitine analogs are used to probe the regulatory interactions between carbohydrate and fatty acid metabolism.

Dr. Inturrisi is developing a scientific basis for the use of opioid analgesics in the management of pain. Research is conducted at the molecular, receptor and patient levels.

The role of neurogenic and hormonal factors in the regulation of mRNA transcription and opioid peptide biosynthesis in CNS and adrenal medullary tissues is being investigated by use of high performance liquid chromatography, tracer techniques and cDNA probes.

Chronic treatment with opioid antagonists increases opioid binding in the central nervous system and produces an increase in the analgesic activity of morphine. Studies are being conducted on the functional and molecular consequences of these effects with respect to dosage, strain and species differences, development of tolerance and dependence, and mediation at spinal and supraspinal sites.

Clinical studies are aimed at developing pharmacologic models from patient data that can be used to improve analgesic therapy and provide insight into the quantitative aspects of the development of tolerance to opioids in these patients. Of special in-

terest are the value of newer opioids, opioid peptides and novel routes of administration in the management of pain in cancer patients.

Dr. Levi examines the possibility that mediators of inflammation and immune hypersensitivity cause cardiac dysfunction and play a role in the pathogenesis of sudden death, heart attacks, and cardiac failure. The molecular bases of the negative inotropic effect of leukotrienes platelet-activating factor and histamine, as well as the electrophysiological and biochemical effects of these mediators are being studied. Further, the relevance of complement activation and anaphylatoxin generation in cardiac hypersensitivity is being investigated. The possible physiological role of endogenous cardiac histamine as a modulator of adrenergic responses is being uncovered. The receptors mediating this histamine-induced modulation are being sought and the molecular mechanisms of this modulation are being assessed.

Dr. Montal's laboratory is interested in the molecular basis for cell communication, signal transduction and excitable ion channels.

Dr. Okamoto studies the pharmacologic and neuropharmacologic bases of the drug independence caused by general central nervous system depressants in adults and neonates exposed to drugs during their fetal period. Barbiturates, benzodiazepines and alcohol are the prototype drugs for these studies.

Ongoing studies involve development of analytical procedures for the determination of sedative-hypnotic drugs and their pharmacologically active metabolites, steroids, biogenic amines, and polypeptides in biofluids; neuroelectrophysiologic and behavioral monitoring of acute and chronic drug actions, investigation of functional and cellular mechanisms for the chronic effects produced to these drugs.

Dr. Pasternak studies the biochemical and pharmacological properties of various subclasses of opiate receptors within the central nervous system. Molecular approaches include binding studies and affinity labeling of receptors using a series of irreversible opiate agonists and antagonists developed and synthesized in this laboratory. Computerized quantitative autoradiographic studies are aimed at the distribution of the various subtypes of receptors complement the biochemical studies. In addition to these molecular studies, the biochemically defined binding subtypes are correlated with specific opiate actions, including analgesia, respiratory depression, gastrointestinal motility and hormone modulation, using classical pharmacological techniques. Again, the selective affinity labels developed in this laboratory have proven invaluable in these studies.

Dr. Reidenberg pursues one of the major questions in clinical pharmacology: Why do different people react differently to the same dose of the same drug? His program in clinical pharmacology addresses this question in a number of ways. He has learned how genetically controlled rates of drug metabolism alter dose-response and has systematically studied how decreasing kidney function modifies drug action. The information gained from these studies has been incorporated into the mainstream of medicine and therapeutics.

The elderly are a class of patients for whom more knowledge about individualization of drug therapy would be useful. A principle abnormality in drug handling by the body associated with aging is the decline in rate of drug excretion because of the decline in kidney function. Data in man and in experimental animals indicate that most individuals "adapt" to continuous exposure to modest levels of nephrotoxic chemicals in their environment. Present research is designed to learn more about this "adaptation" process to gain information about why kidney function declines as people age.

Dr. Rifkind's interest in environmental toxicology has led to the investigation of the biochemical mechanisms of polychlorinated biphenyl and dioxin toxicity. Toxic polychlorinated biphenyls and dioxins are known to bind to a cytosolic and nuclear receptor known as the Ah receptor which controls the expression of a group of gene products, the major one being a form of cytochrome P-450 known as cytochrome P-448. Although induction of hepatic cytochrome P-448 regularly accompanies PAH toxicity it does not directly cause the toxicity. In investigating how receptor activation leads to the various toxic changes, it was found that treatment with toxic PCBs and dioxins increases the hepatic metabolism of arachidonic acid by cytochrome P-450 and also that toxic PCBs and dioxins cause cardiac contractile dysfunction. Current studies focus on the role of arachidonic acid metabolites in producing the toxic manifestations of PCBs and dioxins and the nature of the biochemical changes accompanying the decreased cardiac contractile responsiveness in PCB and dioxin treated animals.

Dr. Sirotnak's research focuses on (1) molecular targets and other cellular biochemical determinants important to selective antitumor action of various categories of cytotoxic antimetabolites; (2) cytoplasmic membrane transport of pharmacologic agents; (3) molecular mechanisms of acquired resistance of tumor cells to antineoplastic agents; and (4) the regulation of folate and nucleoside transporter gene expression.

Folates play a crucial role in the biosynthesis of macromolecules. Access of tumor cells to exogenous plasma folate is made possible by the existence in the cytoplasmic membrane of a specific high-affinity transport system.

Using c-DNA probes, the genetic regulation and molecular biology of this system are now being examined in models which constitutively over-produce or underproduce the transport protein and during induction of tumor cells to terminal maturation.

Folate and nucleoside analogs effectively accumulate in tumor cells via plasma membrane systems normally transporting natural folates and nucleosides. To understand the selective antitumor action of folate and nucleoside analogs, studies are being conducted of the properties and multiplicity of their cellular membrane transport, their interaction with enzymic and macromolecular targets, their intracellular metabolic disposition and their pharmacokinetic behavior. Mechanisms of acquired resistance in tumor cells to these antimetabolites and other cytoxic agents at the level of their cellular membrane transport are also studied by the investigation of alterations.

Dr. Szeto's laboratory is interested in the effects of prenatal drug exposure on the development of the central nervous system, particularly in the development of sleep-wake behavior and the regulation of breathing in the fetus and neonate. As such investigations cannot be carried out in humans, the fetal lamb is used as an animal model. Techniques that permit continuous intrauterine recording of fetal electrocortical activity, eye movements, postural muscle activity, and diaphragmatic activity, resulted in the finding that acute prenatal exposure to opiates and benzodiazepines can alter fetal behavioral and breathing activity. The effects of chronic opiate exposure on the maturation of sleep-wake behavior and respiration control are now being examined.

Another area of study is the effect of maternal marijuana smoking on the fetus by introducing marijuana smoke into the maternal trachea and monitoring its effects on maternal and fetal neurobehavior, hemodynamics, metabolism and hormonal regulation.

In addition, a variety of pharmacologic agents are being used to investigate the role of various neurotransmitters and neuromodulators that may potentially be involved in the regulation of sleep-wake behavior and respiratory control in the fetus.

Dr. Watanabe is interested in synthetic photochemistry to enzyme reaction mechanisms. Major emphasis is on the chemical design and development of better anticancer and antiviral agents which interfere with selective DNA metabolism. On the basis of a biological and biochemical rationale, various sites on the molecules of natural substances and synthetic derivatives with biological activities are chemically modified so that these new molecules may inhibit specific enzyme reaction(s). Recent discoveries of novel carbohydrate reactions have resulted in the development of potent antiviral N-nucleosides. The novel heterocyclic chemistry discovered in this laboratory has been employed in the development of C-nucleosides with potent anticancer activity. Also, these heterocyclic reactions have been applied to the preparation of anticancer antifolates. These findings have led to the proposal of plausible mechanisms of action for tryptophan oxidizing enzyme and cytidine deaminase, on the basis of studies using simple chemically modified substrates.

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Physiology and Biophysics

Faculty

Olaf S. Andersen
Ellen Townes-Anderson
Rodney E. Bigler
Walter W. Y. Chan*
Colin Fell
Daniel Gardner
Marvin C. Gershengorn
Bernice Grafstein
Roger L. Greif (Emeritus)
Chin Ok Lee
Roberto Levi*
Chiann-Tso Lin
Martin Lipkin
Thomas Maack
Lawrence Palmer
Thomas G. Pickering
Enrique M. Rabellino
Barbara Rayson
John P. Reeves
John L. Stephenson
Bernd W. Urban
Alan M. Weinstein
Erich E. Windhager

*Members of the Program in Pharmacology. For representative bibliography, see Pharmacology.

Research Activities

Dr. Windhager's studies are aimed at the elucidation of the mechanisms of ion and water transport by renal epithelial cells. The techniques used in Dr. Windhager's laboratory include: isolated perfused renal tubule segments, intracellular measurement of ions by ion selective electrodes, electrophysiological techniques, isolated membrane techniques and renal micropuncture methods. Current work centers on the role of cytosolic calcium ions as regulators of ion and water transport in proximal tubules and collecting ducts of the kidney. Collaborating with Dr. Windhager are Drs. Heinz, Frindt, Lin and Jones.

Dr. Grafstein investigates nerve regeneration and transport of material in nerve axons. She is currently studying regeneration of goldfish optic nerve. Some of the conclusions reached in recent work are: Phosphorylation of axonally transported proteins is an important function in regeneration; block of physiological activity impairs regeneration by interfering with axonal transport of glycosylated constituents. Dr. Grafstein's laboratory uses the following techniques, among others: isotope tracer studies, electronmicroscopy, high resolution autoradiography, and 2-dimensional gel electrophoresis.

Dr. Maack's studies are directed at the elucidation of the quantitative aspects and mechanisms of renal processing and actions of circulating proteins and peptide-hormones. The main findings in this regard are that the uptake of proteins by proximal tubular cells is a high capacity-low affinity selective endocytic transport process. Disposal of absorbed protein is also a selective process which depends on an appropriate acid pH of lysosomes. The renal processing of low molecular weight proteins and peptide hormones accounts for a major fraction of the plasma turnover of these substances. The results of these studies permitted a better understanding of the

pathophysiology of proteinurias and hormonal disturbances in renal diseases. More recent studies deal with the renal processing and actions of atrial natriuretic factor, a novel hormone secreted by the heart which decreases blood pressure, regulates kidney function and increases salt excretion. The techniques used in Dr. Maack's laboratory include isolated perfused rat kidney, isolated tubule segments, cell culture, receptor-hormone interactions and general biochemical and physiological techniques.

Dr. Andersen is interested in the mechanisms by which ions cross membranes. His studies entail analysis of permeability characteristics of lipid bilayers, with emphasis on the physical and chemical properties of proteins which serve as channel formers. The emphasis of the present work is on structure-function studies of membrane channels using site-specific amino acid substitutions, and on covalent modification of voltage-dependent sodium channels using group specific reagents. Techniques used in Dr. Andersen's laboratory include: single channel analysis, electrophysiological measurements, physico-chemical analysis, and computer simulations.

Dr. Stephenson is interested in theoretical aspects of transport in biological systems. Much of his recent research centers on transport of water and electrolytes in epithelia and in the kidney. One group of current studies focuses on the relation of medullary concentration gradients and the osmolality of final urine in the mammalian kidney to tubular and vascular permeabilities, flows, and architecture. A second project is to develop a mathematical model of electrolyte transport in the whole kidney, which includes electrolytes (Na, K, Cl, HCO_3, H_2PO_4, H), glucose urea, protein osmotic forces, hydrostatic pressure, and electrical potential. Approaches to these problems include both computer simulation and the development and theoretical analysis of mathematical models.

Dr. Gershengorn's laboratory focuses on the understanding of hormonal regulation of cellular secretion. In particular, the stimulation of the anterior pituitary gland's secretion of thyroid-stimulating hormone and prolactin by thyrotropin-releasing hormone is under study. Research is now centered on the inositol lipid-calcium-protein kinase C pathway for signal transduction by TRH.

Dr. Pickering's main area of research is concerned with development of improved methods for the noninvasive measurement of blood pressure. First, he is using ambulatory monitoring techniques to learn more about the causes of blood pressure variability in normal and hypertensive subjects. This work has shown that most of the observed circadian rhythm of blood pressure can be accounted for by changes of activity. Second, he is analyzing the causes and origins of Korotkoff sounds with a view to the development of a new technique for blood pressure measurement.

Dr. Fell studies the reactivity to drugs and other stimuli of microvessels in rat and rabbit ears and rat mesentery, using the technique of ultravital microscopy. The technique has been applied to studies of spontaneous vasomotion in rabbit ear arteries, and to the investigation of the effects of atrial natriuretic factor on vasoconstriction responses of rat mesenteric arteries.

Dr. Gardner's laboratory studies how neurons use chemical synaptic transmission to communicate with one another. He is concerned with the biophysics of synaptic transmission, as well as the properties of neuronal networks. Recent discoveries were: 1) choline activates inhibitory acetylcholine receptors of *Aplysia* buccal ganglia, and 2) dual-function excitatory-inhibitory synapses coordinate the two phases of their postsynaptic potentials by a voltage-dependent change in duration. Techniques used by Dr. Gardner include electrophysiological voltage- and patch-clamping, com-

puter data acquisition and analysis, and artificial intelligence methods for neuronal modeling.

Dr. Lee investigates ionic mechanisms underlying changes in contractile force of cardiac muscle and ion transport across cardiac cell membrane. He recently demonstrated that cardiac glycosides increase cardiac muscle contractility by changing intracellular activities of sodium and calcium ions. Techniques used in Dr. Lee's laboratory include: isolated cardiac Purkinje fibers and intracellular recordings with ion selective electrodes (Na, H and Ca).

Dr. Palmer's research focuses on the mechanism of transepithelial Na reabsorption by tight epithelia, and the control of this process by hormones and other factors. The nature of the transport system facilitating sodium movement across the apical membrane of epithelial cells is being elucidated using the toad urinary bladder and the mammalian cortical collecting tubule as a model epithelia. Techniques used in Dr. Palmer's laboratory include: patch-clamping, current-voltage analysis, and flux ratio analysis.

Dr. Rabellino's research interests are primarily related to the study of the several cellular and molecular processes involved during the acquisition of functional competence by differentiating blood cells. In past studies he has investigated in the lymphoid, myeloid nd megakaryocytic series, the phenotypic evolution of developing marrow cells using monoclonal antibody technology and flow cytometry. Currently, studies are in progress to investigate protein synthesis, cell DNA distribution and synthesis, as well as RNA accumulation in developing megakaryocytes. Studies are also in progress to assess expression and changes of specific protein genes throughout megakaryocytopoiesis using cDNA probes for different alpha granule proteins.

Dr. Reeves' laboratory research is directed toward studying the activity of the sodium-calcium exchange system in membrane vesicles prepared from the plasma membranes (sarcolemmas) of heart cells. The sodium-calcium exchange system is a carrier-mediated transport process which directly couples the transmembrane movement of calcium ions to the movement of sodium ions in the opposite direction. It is thought to play an important role in regulating the force of contraction of cardiac muscle. Previous work has included characterizing the stoichiometry, kinetics and regulation of this transport process. Current efforts are done to identify and purify the membrane protein responsible for this activity.

Dr. Rayson's research activities center on the investigation of the regulation of Na-K/ATPase (Na pump) in kidney cells. Recent discoveries include the finding that intracellular Na levels regulate the number of active Na-K/ATPase enzyme sites in outer medullary tubular segments of the kidney. Current research is directed at the analysis of the cellular mechanisms involved. Techniques used in Dr. Rayson's laboratory include: superfusion of tubular segments of the kidney, protein purification, pulse-chase and in vitro translation experiments.

Dr. Urban studies the molecular actions of general anesthetics on membrane ion channels. He is investigating the mechanisms by which anesthetics change sodium and potassium currents in nerves (squid giant axon) and which effects anesthetics have on single sodium channels (in lipid bilayer systems). Techniques used in Dr. Urban's laboratory include: voltage-clamp, electrophysiological techniques and lipid bilayers.

Dr. Weinstein is interested in the theory of solute and water transport across epithelia and developing a mathematical model of proximal tubular function using computer techniques.

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Requirements and Course Offerings

Memorial Sloan-Kettering Cancer Center and Manhattan Skyline, as seen from Cornell Medical Center.

Admission

Applications

For admission to the Graduate School of Medical Sciences an applicant must (1) have a baccalaureate degree or the equivalent from a college or university of recognized standing, (2) have adequate preparation in the chosen field of study, and (3) show promise of ability to pursue advanced study and research, as judged by his or her previous record.

Inquiries about graduate study should be addressed to the Associate Dean of the Graduate School of Medical Sciences, 1300 York Avenue, New York, NY 10021 or to the Director of the Sloan-Kettering Division, 1275 York Avenue, New York, NY 10021.

Candidates may be admitted in September, February, or July, although places in the graduate program for February and July may not be available because of prior commitments to applicants for September admission. Applicants for February or July admission should correspond directly with the respective Program Director regarding the availability of places.

Application material must be completed and returned to the Office of the Graduate School of Medical Sciences together with (1) official transcripts of records from all colleges and universities attended, (2) a statement of purpose of graduate study, and (3) two letters of recommendation from individuals in academic positions who know the applicant professionally. In addition, scores from the Graduate Record Examinations (GRE) are required to aid in the evaluation of an applicant. Application for taking the Aptitude (Verbal, Quantitative, and Analytical) Test and the Advanced Test of the GRE, must be made directly to the Educational Testing Service, Graduate Record Examinations, Box 955, Princeton, NJ 08541.

The proper Institution Code Number to use in your GRE application for the Cornell University Graduate School of Medical Sciences (New York City) is R 2119-6.

Applications for September or July admission and all credentials, including official transcripts of records from all colleges and universities attended, must be received by the deadline of **February 1.** Because GRE scores are an important part of the application it is of decided advantage to the applicant, to submit these scores by the February 1 deadline.

Applications and credentials for February admission must be received by November 1.

Application fee. A nonrefundable charge of $35 is made for filing an application for admission.

The completed application and all supporting documents are initially screened by the credentials committee of the program to which the student is applying. Applicants who are considered potentially acceptable are usually called for a personal interview. At the time of interview, after discussing his or her interests with the members of the Program, the applicant may tentatively select a major sponsor. If accepted by the Program, an application is forwarded to the Credentials Review Committee and then to the Dean for final decision. A student is formally notified of acceptance for study in the Graduate School of Medical Sciences by a letter from the Dean. An applicant accepted for admission is requested to inform the Graduate School of Medical Sciences of her or his plan to either accept or refuse the offer of admission within one month after the Dean's acceptance letter has been received.

It is the policy of Cornell University to actively support equality of educational and employment opportunity. No person shall be denied admission to any educational program or activity or be denied employment on the basis of any legally prohibited discrimination involving, but not limited to, such factors as race, color, creed, religion, national or ethnic origin, sex, age, or handicap. The University is committed to the maintenance of affirmative action programs which will assure the continuation of such equality of opportunity.

Admission policies are also in conformity with the policy of New York State in regard to the American ideal of equality of opportunity as embodied in the Education Practices Act.

Categories

An applicant is accepted by the Graduate School of Medical Sciences (1) as a degree candidate for the M.S. or Ph.D., or (2) as a provisional candidate.

Provisional candidacy provides opportunity for a prospective degree candidate, whose educational preparation is difficult to evaluate, to begin graduate studies. On the basis of the record of accomplishment in the first half of the academic year, the adviser or

temporary Special Committee of a provisional candidate may recommend to the Dean that (1) provisional candidacy be changed to degree candidacy, (2) provisional candidacy be continued for the remainder of the academic year, or (3) provisional candidacy be terminated. A maximum of one academic year in the status of provisional candidacy is permitted and credit of a maximum of one residence unit may be allowed on petition, provided there is convincing evidence that performance has been of the same quality as that required of degree candidates.

Special Students

Special students are students who are not degree candidates in either the Graduate School of Medical Sciences or the Medical College and who are given permission by the respective dean to take courses at either school. Special students must be degree candidates at other institutions and the courses taken at Cornell must be essential to their degree programs and are not offered by the institutions at which they are matriculated as degree candidates as certified by the institutions. Enrollment as a special student is not intended as preparation for admission to degree programs at Cornell or elsewhere.

In the case of the Graduate School of Medical Sciences, special students are accepted only with the approval of the appropriate Program Director. Special students must demonstrate special qualifications in terms of preparation and ability. They must register with the Graduate School of Medical Sciences or in the Medical College and must pay all tuition and fees before being permitted to attend lectures or laboratory sessions. Tuition is computed on the basis of the ratio of course hours taken to the total hours of instruction for the academic year (33 weeks of 40 hours). There is a registration fee of $35.

Degree Requirements

Major and Minor Programs

A candidate for the degree of Master of Science is required to register for study in one major and one minor program. Each program decides whether the Special Committee of a candidate for the Ph.D. degree must have two or three programs represented. Accordingly, a candidate for the degree of Doctor of Philosophy is required to register for study in one major and one or two minor programs. At least one of the minors must be outside the area of the major program.

The Special Committee

The general degree requirements of the Graduate School of Medical Sciences are minimal in order to give maximum flexibility in choosing a desirable program of study. The student's program is determined with the aid and direction of a Special Committee, consisting of at least three faculty members chosen by the student from those programs that best fit his or her areas of interest. Satisfactory progress toward a degree is judged by the committee rather than by arbitrary standards imposed by the Graduate School of Medical Sciences. There are no regulations of the Faculty of the Graduate School of Medical Sciences governing the specific content of instruction, courses, or grades to which the Special Committee must subscribe, except those imposed by the programs. The committee is primarily responsible for the candidate's development as an independent scholar and scientist.

No later than four weeks after enrollment, a candidate must file a statement of the major and minor programs elected for study, after which the student must choose faculty members to represent the programs and to serve on a Special Committee. The major sponsor usually advises the student concerning the other selections and chairs the committee. At least one member of the committee must represent a program different from the candidate's major program. Members may agree to serve temporarily during the candidate's first year of residence until the candidate has had the opportunity to become acquainted with areas of research in the programs of his or her choice. On completion of this year of residence, a permanent Special Committee will be formed, the membership of which can be changed with agreement of all members of the old and newly formed committees and the approval of the Dean. The members of the Special Committee decide on the student's program of study and research. They judge whether progress toward a degree is satisfactory and prepare term reports on the candidate for submission to the Dean. The members of the committee serve on all the candidate's examining committees and they approve his or her thesis.

Registration and Course Grades

No student in the Graduate School of Medical Sciences may double-register for an advanced general or professional degree with any other school or college except the Cornell University Medical College.

At the beginning of each term, students are required to register with the Office of the Graduate School of Medical Sciences and to file a registration of courses form indicating all courses they will take. A fee of $10 is charged for late registration.

At the beginning of each course in which the student is enrolling, the student will complete a separate course registration form for the instructor. All courses for which the student registers for credit will be entered in the official record. Grades of graduate students are reported as: Excellent (E), Satisfactory (S), Unsatisfactory (U), Incomplete (I), Absent (Abs.), or Unofficially Withdrawn (W). A grade of Incomplete or Absent cannot be changed later than one term following the one in which the course was taken.

Registration for the summer is required of graduate students who will be engaged in research.

Residence

The Faculty of the Graduate School of Medical Sciences regards study in residence as essential. Each candidate for an advanced general degree is expected to complete the residence requirements with reasonable continuity. A student must register each term from the time of his or her first registration in the Graduate School of Medical Sciences until the student either withdraws or completes a degree (unless a leave of absence has been granted). Full-time study for one-half academic year with satisfactory accomplishment constitutes one residence unit. Two units of residence are the minimal requirement for the master's degree and six units are the minimum for the doctoral degree. However, the time necessary to obtain the degree generally exceeds the minimal requirements. A candidate for the Ph.D. degree must spend two of the last four units of required residence in successive terms on the New York City or the Ithaca campus of Cornell University. No more than seven years may intervene between the time of first registration and the completion of all requirements for the doctoral degree. A student must complete all requirements for the master's degree in four years.

Part-time graduate study, if it is necessitated by off-campus employment noncontributory to the major program of study, is not encouraged. Requests for part-time study must be reviewed by the Executive Committee. If permission is granted for part-time study, the student must be in residence at least half-time.

The legislation with respect to eligibility of part-time students for residence units is as follows:

Employment	**Residence Units Allowable Per Half Academic Year**		
Total clock hours per week	*Contributory in major program on campus*	*Noncontributory; on campus*	*Off Campus*
0–10 hours	1 unit	1 unit	¼ unit
11–20 hours	1 unit	¾ unit	¾ unit
21–30 hours	¾ unit (teaching) ¼–1 unit (research)*	½ unit	—

*Time spent assisting in research, if it is contributory to the major program of study, shall be credited toward allowance of a full residence unit.

Transfer of Residence Credit

No residence credit will be granted for study outside the Graduate School of Medical Sciences to fulfill the requirements of the M.S. degree. No commitment can be made about granting residence credit toward the Ph.D. requirements for previous study in another graduate school until after the candidate has entered into residence at the Graduate School of Medical Sciences. At that time, the student's Special Committee may recommend acceptance of study outside the Graduate School of Medical Sciences to the Executive Committee, which will determine the number of residence units to be awarded. No credit can be transferred for study undertaken as an undergraduate or as a special student even in courses designed for graduate students.

A student who has satisfactorily completed two or more academic years of study toward the degree of M.D. at the Cornell University Medical College, or another accredited medical school in the United States with a curriculum equivalent to that of the Cornell University Medical College, may transfer a maximum of two units of residence credit after passing an evaluation examination administered by a committee appointed by the Executive Committee of the Graduate School of Medical Sciences.

Summer Research

Registration is required for the summer research term whether or not this effort will be credited toward residence unit accumulation. Students registered for summer research pay prorated tuition only if they are obtaining residence credit. However, no degree candidate is eligible for more than two residence units in any period of twelve consecutive months.

Study *In Absentia*

A candidate for the degree of Doctor of Philosophy may petition for permission to earn residence units for study away from Cornell University while regularly registered in the Graduate School of Medical Sciences. A candidate to whom this privilege has been granted, must register as a Candidate *in absentia* and may work temporarily under the immediate supervision of an individual designated by his or her Special Committee although the candidate's program will continue to be directed by the Committee. For study *in absentia,* not more than two residence units may be earned toward fulfillment of the minimal residence requirements for the Ph.D. degree.

Leave of Absence

A candidate who finds it necessary to interrupt the continuity of his or her residence must petition the Dean for an official leave of absence. This written petition must specify the term of absence, state the reason for the requested leave of absence, and be approved by the student's Special Committee.

A student who will *not* be in residence but will return to the Graduate School of Medical Sciences to present and defend a thesis at the final examination, having completed all requirements for a degree except for the final examination, *must* petition for a leave of absence.

Examinations

Three examinations are required by the Faculty of the Graduate School of Medical Sciences: (1) Final Examination for the M.S. degree, (2) Examination for Admission to Doctoral Candidacy, and (3) Final Examination for the Ph.D. degree. Examinations are administered by an Examining Committee consisting of a chairperson appointed by the Dean, the members of the candidate's Special Committee, and, in the case of the Admission to Doctoral Candidacy Examination, one additional member selected from the Faculty of the Graduate School of Medical Sciences or of other institutions. In addition to these examinations, the candidate's major program may require a qualifying examination as part of its evaluation of the candidate after two units of residence have been completed.

For the M.S. degree: The Final Examination may be oral or both oral and written.

For the Ph.D. degree: The Admission to Doctoral Candidacy Examination is both oral and written and certifies that the student is eligible to present a thesis to the Faculty of the Graduate School of Medical Sciences. The examination should be taken after course work is largely finished but before significant thesis research has begun. Accordingly, the usual examination time will be at the end of the second year of residence. The examination may not be taken until two units of residence credit have been accumulated and a minimum of two units of residence credit is required after passing this examination before the final examination can be scheduled. The final examination for the Ph.D. degree is an

oral defense of the candidate's thesis. It must be passed within four years after completion of the required residence units, or within seven years from the date of first registration, whichever is earlier.

Foreign Language Requirements

Each program of study has its own foreign language requirements. The student's Special Committee may require knowledge of foreign languages beyond the requirements of the programs listed in this catalog.

Arrangements for a foreign language examination will be made on application to the Office of the Dean. As an alternative to this examination, the candidate may demonstrate proficiency by having passed the reading part of the language qualification tests administered by the College Entrance Examination Board.

Thesis

A principal requirement for both the M.S. and the Ph.D. degrees is the presentation of a thesis constituting an imaginative contribution to knowledge. Ordinarily, the thesis is written on a research topic in the candidate's major field of study, under the direction of the chairperson of his or her Special Committee. The time between the thesis defense and submission of the thesis in its final form is limited to 60 days. The faculty requires that the Ph.D. thesis be published in abstract and be recorded on microfilm.

Tuition and Fees

Tuition

Tuition for a student regularly matriculated in the Graduate School of Medical Sciences is $11,465 for the academic year 1987–88 and is payable in two equal parts, the first of which is due at initial registration. Tuition includes fees for matriculation, hospitalization insurance, graduation, and miscellaneous thesis expenses.

Students in the Ph.D.-M.D. program (see p. 4) will be charged Medical College tuition ($16,300 per annum) while they are enrolled in medical school.

A student who is to receive partial residence credit (see p. 52) because of employment should apply for proration of tuition on forms obtainable at the Office of the Dean.

Other Fees

In Absentia A student registered *in absentia* pays a fee of $200 each term and may continue hospitalization insurance by payment of the annual premium directly to the Student Accounting Office. If students *in absentia* take advantage of local privileges, such as the use of the library, desk space, Student Health Service, and Cornell housing, the fee is $400 per semester. The latter fee also covers hospitalization insurance.

Leave of Absence Students on leave of absence will be required to pay an active-file fee of $200 for each semester, up to a maximum of six semesters, during which they are not registered with the Graduate School. This fee will not be subject to finance charges but must be paid before the student can receive an advanced degree. Petition for waiver of this fee will be considered for students who have not completed the required number of residence units.

Candidate for Degree Only A graduate student who has previously fulfilled all other degree requirements, who has been granted a leave of absence, and then returns to the Graduate School of Medical Sciences to present a thesis and to take the final examination must register as a Candidate for Degree Only and pay a fee of $35.

Any individual who owes money to the University will not be allowed to register or reregister in the University, receive a transcript of his or her record, have his or her academic credits certified, be granted a leave of absence, have a degree conferred and will not be eligible for health services and subsidized housing.

The amount, time, and manner of payment of tuition, fees, or other charges may be changed at any time without notice.

Refunds

Part of the *personally* paid tuition will be refunded if the student obtains official certification of leave of absence or withdrawal from the Graduate School of Medical Sciences during the semester. Students who terminate their registration during a regular term in this manner will be charged tuition from the registration day to the effective date of the certificate as follows: first week, 10 percent; second week, 20 percent; third week, 30 percent;

fourth week, 40 percent; fifth week, 60 percent; sixth week, 80 percent; seventh week, 100 percent. No charge will be made if the effective date of leave or withdrawal is within the first six days of the term, including registration day.

Financial Assistance

All applicants to the Graduate School are requested to submit a Graduate and Professional School Financial Aid Service (GAPSFAS) form providing an estimate of financial need. The information will be used in two ways: The number of students with documentable need will allow the University to obtain maximum federal funding for loans and work-study purposes, and the specific need of an applicant *may* be used to determine that individual's graduate support. Please obtain the necessary form, available at your college or university financial aid office and from the Educational Testing Service. File the form with the Educational Testing Service, Box 2614, Princeton, New Jersey 08541, and request that the information be sent to Cornell-Code 2267.

Financial assistance is available to qualified applicants. Individual fields may offer predoctoral research fellowships, research assistantships, or teaching assistantships. These positions may provide a stipend in addition to tuition. Information about these positions may be obtained directly from the Program Director at the time of application.

Nationwide competitive predoctoral fellowships are available from the National Science Foundation and the National Research Council. Information about these fellowships should be requested directly from the appropriate governmental agency.

New York State residents are eligible for several predoctoral fellowships and the Tuition Assistance Program, which assists in tuition payments. Application forms may be obtained from the New York Higher Education Services Corporation, Student Financial Aid Section, Tower Building, Empire State Plaza, Albany, NY 12255.

Several loan programs are available to graduate students. Under these programs, repayment of the principal amount of the loan together with the interest on the loan may be deferred until after graduation. Complete information regarding loan programs may be obtained from the Graduate School Office.

Opportunity for part-time employment is often available in departmental research projects or other activities. Applications should be made directly to individual departments.

The Graduate School of Medical Sciences participates in the Work-Study Program of Cornell University which provides a significant salary contribution for qualified employed students.

Scholarships and Fellowships

Full fellowships are provided for graduate students by both the Medical College and Sloan-Kettering Divisions of the Graduate School of Medical Sciences. Recipients of this award become Ph.D. Fellows and will receive a full tuition scholarship and a stipend covering living expenses.

A number of tuition scholarships are available for students in the Medical College Division who are not covered by one of the above fellowships. This scholarship fund is administered by the Office of the Dean of the Graduate School of Medical Sciences.

In addition, the following named funds provide support for selected students:

The Vincent Astor Scholarship Fund. Funds for tuition assistance are also derived from the income from a generous gift by the Vincent Astor Foundation to the Graduate School of Medical Sciences and to the Medical College. Allocation of these funds for graduate student tuition assistance is made at the discretion of the Dean of the Graduate School of Medical Sciences.

The Harry E. Gould, Sr., Medical and Graduate Student Scholarship. This fund was established by Mr. Gould's son, Harry E. Gould, Jr., in memory of his father, a prominent business and civic leader in the City of New York, who had a long-standing interest in medicine. The income from this endowment provides financial assistance for students of the Medical College and Graduate School of Medical Sciences.

The Mildred and Emil Holland Scholarship. Income from a gift by the Emil and Mildred Holland Philanthropic Fund of the Jewish Communal Fund is used to provide tuition support for an M.D.-Ph.D. student.

The W. A. Keck Foundation Medical Scientist Fellowship. This award is derived from a generous endowment awarded to Cornell University Medical College and provides support for an M.D.-Ph.D. student.

The Francis L. Loeb Medical Scientist Fellowships. These fellowships have been endowed by a gift from Francis L. Loeb and provide support for two M.D.-Ph.D. students at the Cornell University Medical College.

The Frank R. and Blanche A. Mowrer Memorial Fund. Financial assistance is available from the income of this fund to one student each year enrolled in the Ph.D.-M.D. or M.D.-Ph.D. program.

The Papanicolaou Medical Scientist Fellowship is funded by income from a bequest from Mary G. Papanicolaou in memory of her husband, Dr. George N. Papanicolaou, and by a gift from an anonymous donor to the Cornell University Medical College. The funds provide support for an M.D.-Ph.D. student.

The Abby Rockefeller Mauzé Medical Scientist Fellowship was established by a gift from the Abby Rockefeller Mauzé Trust. The income provides fellowship support for an M.D.-Ph.D. student.

The Surdna Foundation Medical Scientist Fellowship was made possible by a generous grant to the Medical College by the Surdna Foundation. The income from this endowment provides fellowship support for an M.D.-Ph.D. student.

Awards and Prizes

The Julian R. Rachele Prize. The income of a fund established by Dr. Julian R. Rachele, former Dean of the Cornell University Graduate School of Medical Sciences, provides for an annual prize to be awarded to a candidate for the Ph.D. degree for a research paper of which the candidate is the sole or the senior author.

The prize was shared in 1987 by Robert Hariri and David Russell.

The Vincent duVigneaud Prizes for the presentation of outstanding papers by students of the Cornell University Graduate School of Medical Sciences at the Annual Vincent duVigneaud Memorial Research Symposium.

Recipients of these awards in 1987 were Corinne Abate, Rafael Fernandez-Almonacid, and Beatrice Knudsen.

The Frank Lappin Horsfall Jr. Award is endowed by funds provided in memory of Dr. Horsfall by his many friends and family. It is continued evidence of his concern for students manifest during his directorship of the Sloan-Kettering Division.

The award is made annually to a student of the Sloan-Kettering Division, who in the opinion of the Committee of the Faculty of the Sloan-Kettering Division, has been most distinguished, especially in the Admission to Doctoral Candidacy Examination.

Recipient of the award in 1987 was Clifford Hume.

The Thesis Prizes are awarded to students of the Medical College Division who have presented an outstanding thesis during the academic year.

Recipients of these prizes in 1986–87 were Lynn Doucette and Robert Hariri.

Student Health Services

The student Health Plan of Cornell University Medical College provides hospitalization and major medical insurance for all registered graduate students. In addition, the Plan provides for ambulatory care at the Personnel Health Service of The New York Hospital-Cornell Medical Center. Physicians at the Health Service will refer students who require specialized care to clinics of the Hospital and to attending physicians of the staff.

The cost of medical services provided by the Plan are included in the tuition and fee structure announced by the Graduate School of Medical Sciences each academic year. Students will be issued Plan membership cards and will receive courtesy privileges at The New York Hospital Pharmacy.

Entering students are requested to have a physical examination, chest X-ray and laboratory tests performed by their personal physicians prior to matriculation. The hours of the Personnel Health Service and a complete statement of Plan benefits will be provided to each graduate student.

It is recommended that students purchase insurance coverage for eligible dependents who do not have other insurance available to them. Insured dependents are not eligible for care at the Personnel Health Service but they will be referred to appropriate members of the Hospital staff for medical treatment.

A student studying *in absentia* may continue hospitalization insurance by payment of the annual fees directly to the Student Accounting Office.

A student on leave of absence is not eligible to receive student health benefits.

Residence Halls

F. W. Olin Hall, a student residence, is at 445 East Sixty-ninth Street directly across from the Medical College entrance on York Avenue. Olin Hall contains a gymnasium, lounges, and 245 residence rooms. Each residence room is a single bedroom-study, but since two rooms share a connecting bath, they may be used as a suite for two students. The rooms are completely furnished. The student housing fee is $213 per month.

Livingston Ferrand Apartments, also located on East Sixty-ninth Street, just beyond Olin Hall, have furnished apartments of 1½, 2, 3, and 4 rooms. Cooking facilities are provided in these apartments. Housing fees range from $272–$501 per month (utilities not included). These apartments are available to married and upper-class students.

Jacob S. Lasdon House, an apartment residence, is located at 420 East Seventieth Street. This building contains studio, one-bedroom, and two-bedroom apartments and two squash courts. Apartments are fully furnished and include kitchens. Housing fees range from $460–$1,046 per month including utilities. Single, first-year students cannot be accommodated in this building.

The fees listed above may be changed at any time without previous notice.

Special Programs

Application to the Medical Scientist Training Program (M.D.-Ph.D.)

Successful applicants must demonstrate a strong undergraduate science preparation, and an early commitment to a career combining both clinical and laboratory research. They must simultaneously satisfy the separate requirements for admission to Cornell University Medical College and to the Divisions of the Graduate School of Medical Sciences.

Applications must show whether admission is sought to the M.D.-Ph.D. program of the Medical College Division, the Sloan-Kettering Division, or both (see p. 3 for a description of the programs). Only one set of documents is required for applications to either or both programs. All documents must be forwarded to the *Office of Admissions, Cornell University Medical College, 445 East 69th Street, New York, NY 10021.* Telephone (212) 472-5673.

The following items are required, by November 30, for an application to be considered complete:

1. *AMCAS application.* (The personal data and academic record presented in this application are suitable for evaluation by both the medical and graduate schools.)
2. *Supplemental Information Form.* This form will be supplied when further information is requested.
3. Test Scores. MCAT scores are required; GRE scores are optional. If the GRE is taken, please instruct the Educational Testing Service to forward your scores.
4. *Personal statement.* A summary of the applicant's background, interests, and reasons for pursuing the combined program.
5. *Letters of Recommendation.*
   a. Evaluation by the pre-medical advisory committee or two letters from members of the undergraduate science faculty addressing themselves to the applicant's suitability for a career in medicine.
   b. Evaluations by at least two faculty members addressing themselves to the applicant's research potential.
6. *Application Fee.* After the AMCAS application is received, a check for $45 is requested to cover the application processing fee.

After screening, selected applicants to the program will be invited to visit the Cornell Medical Center and meet with members of the faculty of the medical and graduate programs. These interview visits will be coordinated by the Medical College Admissions Office.

Application to the Ph.D.-M.D. Program

Applications to this program (see p. 4 for description) are ordinarily made after the completion of the first year of study in the Graduate School of Medical Sciences, although more advanced students may be considered. The deadline for application is January 1.

To apply, the student must submit to the Office of the Dean of the Graduate School of Medical Sciences:

1. A completed application for admission with advanced standing to Cornell University Medical College (obtainable from the

Medical College Admissions Office).

2. A plan of graduate study incorporating all required course work of the first two years of the Medical College curriculum and endorsed by the student's Special Committee.
3. Evidence of successful completion of at least two major medical school basic science courses (anatomical sciences, biochemistry, microbiology, pathology, pharmacology, physiology).
4. Two letters of evaluation from faculty of the Graduate School of Medical Sciences.

The Office of the Dean of the Graduate School of Medical Sciences will review the student's credentials and make a recommendation to the Committee on Admissions of Cornell University Medical College. Only applicants who are found to be acceptable by this committee, after review of the application and personal interviews, can enter the Ph.D.-M.D. Program. Final decision will be made before June 1.

Students in this program must meet the following requirements before admission to the third-year clinical curriculum of the Medical College:

1. Complete all required graduate courses and the remainder of the first two years of the medical school curriculum.
2. Pass the Admission to Doctoral Candidacy Examination, required by the Graduate School of Medical Sciences.
3. Complete the dissertation research; present and successfully defend an original thesis at the final examination for the Ph.D. degree.

After satisfactory fulfillment of the required clinical rotations of the Cornell third-year medical school curriculum and of the required selectives of the fourth-year curriculum these students may receive credit for their graduate studies to satisfy the elective requirements of the fourth-year medical school curriculum and will then be recommended for award of the M.D. degree by Cornell University.

While registered as a graduate student in the Ph.D.-M.D. Program, the student is subject to the tuition schedule of the Graduate School of Medical Sciences. Upon completion of the requirements for the Ph.D. degree, the student is registered in the Medical College and is subject to its tuition schedule.

Graduate Seminar

This school-wide seminar is offered weekly each year. Second-year students present brief reports on their research experiences in their laboratory rotations. First-year students may report on laboratory rotations, review a selected area of research, or critically review a research paper. The discussion is carried out principally by graduate students under the guidance of their major (temporary or permanent) sponsors. From time to time outstanding authorities are invited as guest speakers. In addition, students in their third and later years of graduate study address the seminars on the progress being made on their thesis work.

Biochemistry

Graduate Program Chairman

A. Meister, Department of Biochemistry, Room E-106, Medical College, (212) 472-6212

Graduate Program Director

D. Wellner, Department of Biochemistry, Room E-219, Medical College, (212) 472-6197

Graduate instruction is offered leading to the Ph.D. degree. Within the framework of degree requirements and in consultation with the student, the course of study is planned to fit the need of the individual. Although formal course work is required, emphasis is placed on research. Research opportunities exist in various areas of biochemistry including enzymology, structure and function of proteins and nucleic acids, molecular biology, physical biochemistry, and the intermediary metabolism of amino acids, carbohydrates, nucleic acids, and lipids. Entering graduate students usually work for short periods in several of the laboratories of the faculty members of the Field before beginning their thesis research. Students are encouraged to choose challenging fundamental research problems that are on the frontiers of biochemistry.

The laboratories of the faculty members are equipped with virtually all of the instruments and facilities required for modern biochemical research; thus, graduate students are instructed in such methodology as chromatography, countercurrent distribution, radioactive and stable isotope techniques, spectrophotometry, electrophoresis, and analytical ultracentrifugation.

Students who undertake graduate study in biochemistry must have a sufficiently comprehensive background in chemistry to pursue the proposed course of study and must present evidence of knowledge of biology, general experimental physics, mathematics (including differential and integral calculus). Students may remedy deficiencies in these areas during the first year of graduate study. The Graduate Record Examination (the aptitude test and the advanced test in chemistry) is ordinarily required.

The student is required to demonstrate proficiency in one modern foreign language acceptable to the student's Special Committee. Proficiency in a computer programming language, as demonstrated by executing a meaningful program, may substitute for proficiency in a foreign language.

Courses

Graduate Biochemistry. Offered jointly by the faculties of the Medical College and Sloan-Kettering Divisions. This course is designed to provide the student with a knowledge of the fundamentals of biochemistry and an appreciation of the molecular basis of biological phenomena. Graduate students in the Field of Biochemistry are required to pass this course (or its equivalent). First and second quarters annually. Dr. Haschemeyer.

Advanced Biochemistry. This course consists of one or more lecture series (mini-courses) covering selected areas of current interest at an advanced level. The topics change from year to year and may be repeated after 2 or 3 years. The subjects offered include: 1) nucleic acids and protein synthesis; 2) intermediate metabolism and its regulation; 3) kinetics and enzyme mechanisms; 4) protein and peptide microchemistry; 5) membrane structure and function; 6) hormones; 7) computer programming for the biochemist; 8) physical methods in the study of macromolecular and cellular structure; 9) design of inhibitors of enzymes and transport systems. Prerequisite: Graduate Biochemistry. Courses offered in 1987–88:

Biosynthesis, Processing, and Intracellular Transport of Proteins. Fourth quarter. Dr. Tate.

Membrane Biochemistry. Fourth quarter. Dr. Hajjar.

Other Academic Offerings

Introduction to Research. Laboratory rotations in experimental biochemistry dealing with the isolation, synthesis, and analysis of substances of biochemical importance (enzymes, co-enzymes, various metabolites and intermediates), and study of their properties by various chemical and physical techniques. The student obtains this varied research experience by spending approximately two months in the laboratory of each of four faculty members of his or her choice. For incoming graduate students majoring in biochemistry.

Biochemistry Seminars. A seminar series in which students, faculty, and invited scientists from this and other institutions report on progress in their laboratories.

Cell Biology and Genetics

Graduate Program Co-Chairpersons

June L. Biedler, Sloan-Kettering Institute, Walker Laboratory, Room 2127, 145 Boston Post Road, Rye, NY 10580, (914) 698-1100, ext. 210

Donald A. Fischman, Department of Cell Biology and Anatomy, Room A-112, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, (212) 472-6400

Graduate Program Co-Directors

Paula Traktman, Department of Cell Biology and Anatomy, Room A-303, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, (212) 472-2516

David B. Donner, Sloan-Kettering Institute, Howard Laboratory, Room 909, 1275 York Avenue, New York, NY 10021, (212) 794-7871

The Program in Cell Biology and Genetics offers advanced study leading to the Ph.D. degree. The program is intended to prepare students for a career in basic research and teaching in cell, developmental and molecular biology, genetics, endocrinology, or related health sciences.

Course Requirements: In the first two years students are expected to complete a core curriculum of Graduate Biochemistry, Cell Biology, Molecular Genetics and Graduate Seminar. To satisfy the requirements for the Ph.D., the students select eight quarters of elective courses with emphasis in either Cell Biology or Genetics. Admission to elective courses in the area of Genetics is predicated upon demonstrated competency in basic genetics.

Laboratory Rotations: Students rotate through three laboratories during the first year. Such rotations familiarize students with ongoing research in the Program and provide a mechanism for selection of the thesis sponsor.

Admission to Doctoral Candidacy: The program administers the Admission to Doctoral Candidacy Examination before the end of the second year of residence. The specific format of the examination, which is composed of written and oral sections, is determined by the examining committee.

Courses

Advanced Cell Biology. Advanced course covering topics in membrane biology, cytoskeleton and cell motility, muscle cell biology, and aspects of nuclear structure and chromosome organization. The course includes lectures and group discussions of assigned research papers. Prerequisite: previous background in basic cell biology or course director's approval. Offered in alternate years. Second and third quarters in 1987–88. Dr. Rodriguez-Boulan and staff.

Molecular Genetics. The class focuses on key topics of molecular biology concerning gene structure and organization in prokaryotes and eukaryotes, chromosome structure, protein synthesis and translational and transcriptional control. The use of genetic, biochemical and molecular biological methods to study the questions experimentally is covered in depth. Some topics of current interest such as immune diversity, oncogenes and homeotic genes are also covered. The course includes an equal number of lectures and in-depth small-group discussions of representative research papers from the current litera-

ture. Prerequisite: background in biological sciences. Limited to 30 students. Offered every year with alternating faculties. Offered during the first and second quarters of 1987–88 by Drs. Jack, Lustig and Osley (Sloan-Kettering Division); offered first and second quarters of 1988–89 by Drs. Chao, Neff and Traktman.

Genetics. A series of electives on advanced topics in human genetics will be offered. Topics may include cytogenetics, population genetics, genetic epidemiology and somatic cell genetics. Drs. Chaganti, German, Jacobs, Morton, Siniscalco and staff. A basic knowledge of genetics will be presumed; scheduling to be arranged.

Graduate Student Seminar. This course is designed to improve graduate students' skills in public presentation. On a rotating basis, students prepare a brief written abstract and an oral presentation on a topic of their choice. The presentation is informally critiqued by the faculty. First through fourth quarters, annually. Dr. Chao and staff.

Developmental Biology. Principles of descriptive, experimental, and molecular developmental biology are presented, using several animal systems as examples. Early development of the whole organism, and of cells, tissues, and organs are considered. Prerequisites: consent of the faculty. Limited to 15 students. Offered in alternate years; third and fourth quarters in 1988–89. Drs. Bachvarova and Bader.

Practicum in Electron Microscopy. A workshop in practical aspects of electron microscopy. Following a weekly one-hour lecture, students conduct specific protocols involved in electron microscopy. Topics covered include: tissue fixation, embedding and thin sectioning; transmission and scanning electron microscopy; shadow-casting of proteins and nucleic acids; immunocytochemistry; photography. All participants are required to complete an independent project. Prerequisite: Consent of instructors. Requirements for passing grade: Completion of an independent project paper. Limited to 10 students. Offered in 1987–88 during third and fourth quarters. Mr. Dennis, Dr. Fischman and staff.

Cell Biology and Microscopic Anatomy. Offered by the staff of the Program in Cell Biology and Genetics in conjunction with the Faculty of the Cornell University Medical College. This course follows a cellular and differentiative approach aimed at understanding the structure-function correlates that characterize the different tissues and organs. Selected topics are presented in the lectures and laboratory exercises to indicate a pattern of study and depth of analysis that the student can be expected to apply to the study of cells and tissues. A microscope slide collection, presenting tissues and organs in a variety of physiological and developmental states, as well as correlative electron micrographs, are provided for individual study in the laboratory. Second and third quarters, annually. Drs. Bader and Wall.

Gross Anatomy. Regional anatomy is studied principally through dissection of the human body. Supplementing this technique are prosections by instructors, tutorial group discussions, and radiographic and endoscopic demonstrations. Enrollment is limited and students should consult the staff early in order to determine the availability of places. First and second quarters, annually, Drs. Hagamen and Weber, and the staff.

Other Academic Offerings

Endocrine Research in Progress Seminars. Reports of ongoing research by faculty of the Graduate School of Medical Sciences, Cornell University Medical College and The Rockefeller University are given weekly throughout the year.

Immunology

Graduate Program Chairman

Osias Stutman, Sloan-Kettering Institute, Kettering Laboratory, Room 1118, 1275 York Avenue, New York, NY 10021, (212) 794-7475

Graduate Program Director

Robert W. Knowles, Sloan-Kettering Institute, Schwartz Laboratory, Room 1001, 1275 York Avenue, New York, NY 10021, (212) 794-7089

The program of study is developed for each student individually on the basis of the student's interest and prior experience. The Immunology Program has no fixed course requirements, but students generally take a core of formal courses offered by the graduate school in immunology, biochemistry, molecular biology, cell biology and genetics in

order to complement their previous background and fulfill their own academic objectives. Participation in a graduate student seminar course is expected of all students to provide experience in oral presentation. Admission to Doctoral Candidacy at the end of the second year requires both written and oral examinations of the candidate's general understanding of immunology and related subjects which are relevant to the proposed research. However, the main focus of the graduate program in immunology is on laboratory research. Each student is required to undertake at least two minor research projects with different faculty members prior to developing a major research proposal for the doctoral thesis. This allows for laboratory experience to begin during the first year of the student's program. By the third year the doctoral candidate begins a full-time thesis project which typically takes two to three years. During this time the student will not take formal courses but will continue to participate in the other educational programs offered by the Institute. These include a wide variety of research seminars which are offered throughout the year with speakers from outside the Institute. In addition, the Immunology Program offers a series of colloquia on current topics in immunology with presentations and discussions led by Immunology faculty members.

Applicants should have a strong undergraduate background in the biological sciences, including biochemistry, molecular genetics, and microbiology and are also expected to have some undergraduate laboratory research experience. The application requires a personal statement describing the student's background and specific interest in the Immunology Program. An official transcript of the student's undergraduate record is also necessary with at least two letters from faculty members who can evaluate the academic potential of the student in a Ph.D. program in Immunology. Applicants must also submit the results of the Graduate Record Exam including the advanced test in Biology or Chemistry.

Courses

Introduction to Immunology This course provides a broad introduction to the field of Immunology and the specific research interests of the faculty. It is designed for first-year graduate students and others with no formal training in Immunology. It includes an overview of the immune system, but also covers selected topics in detail.

These topics include techniques in immunology, B lymphocytes, immunoglobulins and monoclonal antibodies, T lymphocytes and T cell clones, immunogenetics of lymphocyte differentiation antigens, cell mediated immunity, T cell antigen receptors, natural cytotoxicity, macrophage and other accessory cells, lymphokines, the major histocompatibility complex genes and transplantation, HLA and disease associations, and tumor immunology. Quarters I and II, annually. Dr. Knowles and the Immunology Program Faculty.

Other Academic Offerings

Colloquia in Immunology Informal sessions are held monthly between students and senior faculty members to acquaint students with the major research programs headed by each of the faculty members of the Immunology Program.

Molecular Biology

Graduate Program Chairman

Kenneth I. Berns, Department of Microbiology, Room B-308, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, (212) 472-6540

Graduate Program Director

Kenneth J. Marians, Sloan-Kettering Institute, Kettering Laboratory, Room 820A, 1275 York Avenue, New York, NY 10021, (212) 794-5890

Admission A good background in genetics, molecular biology, chemistry, or biochemistry is required of students. Graduate Record Examination scores in both the aptitude test and the advanced test in biology or chemistry are also required.

Course Requirements Students must complete a core sequence of Graduate Biochemistry, Molecular Genetics, and Eucaryotic Gene Structure and Function during their first two years and Graduate Research Seminar throughout their enrollment. To complete the course requirements, eight additional quarter-equivalents of coursework must be taken, chosen from a list of courses approved by the Curriculum Committee. This list currently includes: Nucleic Acids Enzymology, Cell Biology, Developmental Biology, Molecular Virology, Molecular Parasitology, Molecular Biology of Growth Control and Neoplastic Transformation, Electron Microscopy, and Immunology.

Laboratory Rotations Students are required to rotate through a minimum of two laboratories. Laboratory rotations begin immediately after an intensive series of lectures by the faculty designed to familiarize students with the research underway in their laboratories. Rotation periods are: October–January, February–May, June–August. It is expected that students will have chosen their thesis mentor by the start of their second year in the program.

Admission to Doctoral Candidacy This examination will be given once a year in June and consist of two parts, a uniform written exam and an oral defense of a written research proposal. The proposal cannot be in the same field as the student's thesis research. It is expected that most students will take this exam at the end of their second year.

Special Committee A student's Special Committee will be chosen by the student's mentor in consultation with Curriculum Committee when the student elects a laboratory for thesis research.

Curriculum Committee This committee, chaired by the Program Director and consisting of 8–10 members of the faculty, oversees all educational aspects of the program. The committee is responsible for assembling the curriculum, setting course requirements, adjudicating student applications for exemption from course requirements, and the composition and administration of the Admission-to-Candidacy Examination.

Courses

Eukaryotic Gene Structure and Function: A semester-long course presenting the fundamentals of eukaryote gene structure, expression and regulation. Topics discussed include: DNA sequence organization, chromatin structure, viral and cellular RNA transcription, translation and its regulation, control of gene expression in model systems and molecular aspects of carcinogenesis. Third and fourth quarters, annually. Drs. Sen, Sheffery, and staff.

Nucleic Acids Enzymology: A formal course presenting the enzymological mechanisms and control of prokaryotic and eukaryotic transcription and DNA replication. Enzymes which alter DNA structure and shape are reviewed and topics in DNA repair and recombination are also covered. Graduate Biochemistry is a prerequisite. First and second quarters, 1987–88. Alternate years. Drs. Marians, Hurwitz, and Holloman.

Molecular Virology: A formal course in which major emphasis is placed on the basic mechanisms in the biology of all animal viruses, including RNA and DNA tumor viruses. The topics considered include virus structure and composition, assay of viruses and viral-specific products, transcription and replication of viral nucleic acids, translation of virus-specific proteins, assembly of viral particles, structural and functional alterations in viral-infected cells including transformation, pathogenesis of viral diseases, and viral genetics. Third and fourth quarters, alternate years (next offered in Spring, 1989). Drs. Krug and Berns.

Molecular Genetics: This course is designed to familiarize graduate students with practical problems in current research and to encourage critical reading of the scientific literature. Students receive reading assignments and are expected to present short summaries of important experiments at each class meeting. Topics covered include protein structure, protein-nucleic acid interactions, models for transcription factors, genetic complementation, and mapping and suppressor analysis in bacteria and yeast. First and second quarters, annually. Drs. Traktman, Chao, and Neff.

Molecular Biology of Growth Control and Neoplastic Transformation: This course focuses on current efforts to understand the neoplastic cell phenotype from a molecular point of view. The effects of RNA and DNA tumor viruses on host cells are discussed, in particular the transformation and/or differentiation blocks of defined cell lineages by certain agents. The nature and enzymatic specificities of viral gene products responsible for transformation are compared with related products of normal cellular genes. The potential interaction of such products with regulatory systems controlling cell shape, adhesiveness, motility, and mitosis are described, as well as the possible involvement of the same systems in nonviral neoplasias. A section of the course is devoted to the molecular biology and biochemistry of cell surface growth factor- and polypeptide hormone-receptors and mechanisms of signal transmission across biological membranes. At least part of the course consists of student presentations on relevant subjects. Third and fourth quarters, 1987–88. Alternate years. Drs. Hayward, Rosen, Besmer and staff.

Molecular Parasitology: This course focuses on the recent advances in the molecular and biochemical analysis of parasite physiology and their interactions with vertebrate hosts. Lectures are offered once a week, fol-

lowed by a discussion group. Topics include structures and functions of surface molecules, mechanism of antigen variations and immune evasion, interaction of parasites with targeted cells as well as general aspects of gene organization and expression in various parasites. Third and fourth quarters, 1987–88. Alternate years. Dr. Ravetch.

Graduate Research Seminar: This course represents an opportunity for all the faculty and students of the program to hear the upper-class students describe their research in formal seminar presentations. Quarters I–IV, annually. Drs. Lacy and Rosen.

Neurobiology and Behavior

Graduate Program Chairman

Tong H. Joh, Department of Neurology, Cornell University Medical College, Kips Bay Building, Room KB-104, 411 E. 69th Street, New York, NY 10021, (212) 472-4699

Graduate Program Director

Gary E. Gibson, Department of Neurology, Cornell University Medical College, Burke Rehabilitation Center, 785 Mamaroneck Avenue, White Plains, NY 10605, (914) 948-0050, ext. 2291

The Program in Neurobiology and Behavior provides training in the study of the nervous system. It includes the disciplines of neuroanatomy, neuroembryology, neurophysiology, neuropharmacology, neurochemistry, neuroendocrinology, molecular biology, and neuropsychology and perception. The program emphasizes a multidisciplinary approach to the study of the nervous system, based on the belief that future advances in our understanding of the nervous system will be derived from the thinking and research techniques employed by more than one discipline. Toward this end, the program of entering students is planned in consultation with several staff members, and the students are expected to spend some period of time working closely with members of the faculty whose interests are related to theirs. In addition, there are regularly scheduled seminars during which various aspects of work in process are presented and discussed. By these means, the students are afforded the broadest possible view of the program during their total training experience.

The student majoring in Neurobiology and Behavior will be required to satisfy the requirements of the courses in neuroscience, statistics, and biomathematics, and two in the following areas: microscopic anatomy, physiology, biochemistry, and pharmacology. The student must also have two minors, at least one of which is outside the program. In addition, participation in the seminar program and advanced course offerings is expected. While there are no language requirements, it is suggested that the student achieve mastery of a modern foreign language or a computer programming language. The student choosing Neurobiology and Behavior as a minor is required to participate in the neuroscience course and the seminar program as well as obtain any additional experience that the minor sponsor may suggest.

Applicants to the program are expected to have had adequate undergraduate training in biology, organic chemistry, physics, and mathematics. Graduate Record Examination scores are to be submitted with the application. An interview with the applicant is considered highly desirable.

Courses

Neuroscience This is the basic undergraduate medical school course and is required of all major and minor candidates in the program. it is a broadly based course and introduces the student to neuroanatomy, neurophysiology, and pertinent neurology. Fourth quarter annually. Drs. Brooks and Grafstein.

Neuroscience Seminar Current topics of neurosciences, not included or minimally covered in the Neuroscience course, are examined in detail. The course is required of all major candidates in the program. Fourth quarter annually. Drs. Brooks and Grafstein.

Neuropharmacology (see Program in Pharmacology).

Behavioral Neuroscience The aim of this course is to examine the neural substrates of a variety of behavioral and mental processes, including attention, perception, learning and memory, emotion, and language. Anatomical, physiological, pharmacological, biochemical, and molecular mechanisms of normal and pathological behaviors will be covered. The course will be divided into 4 lectures on basic mechanisms and 4 seminars exploring methodological and theoretical issues in contemporary behavioral neuroscience. First quarter, 1987–88. Drs. LeDoux and Mann.

Neurochemistry This course will concentrate on the dynamics of neurotransmitter-amino acid, calcium and energy metabolism of the brain. The emphasis will range from in vivo studies in man and animal that relate directly with behavior to purely chemical approaches. First quarter 1987–88. Dr. Gibson.

Molecular Neurobiology The aim of this course is to introduce current topics of rapidly developing molecular biology research in neurosciences. Topics include basic concepts and techniques, structures of genes encoding neuron specific proteins and enzymes, and gene expression in neuronal cells. Second quarter, 1987–88. Dr. Joh.

Pharmacology

Graduate Program Co-Chairmen

Joseph R. Bertino, Sloan-Kettering Institute, Schwartz Laboratory, Room 1001C, 1275 York Avenue, New York, NY 10021, (212) 794-8230.

Walter W. Y. Chan, Department of Pharmacology, Cornell University Medical College, Room E-400, 1300 York Avenue, New York, NY 10021, (212) 472-6029

Graduate Program Co-Directors

Michiko Okamoto, Department of Pharmacology, Cornell University Medical College, Room E-411, 1300 York Avenue, New York, NY 10021, (212) 472-5875

Francis M. Sirotnak, Sloan-Kettering Institute, Kettering Laboratory, Room 316, 1275 York Avenue, New York, NY 10021, (212) 794-7952

The Graduate Program in Pharmacology is jointly sponsored by faculties of the Medical College Division and Sloan-Kettering Division. This coordinated faculty provides the student with a broad spectrum of challenging research opportunities in modern pharmacology and a unified curriculum. Students admitted to this program will receive tuition scholarships and stipends.

Admission A baccalaureate degree with a strong background in the natural sciences and/or health sciences is required for admission. Graduate Record Examinations in both the aptitude test (verbal and quantitative) and the advanced test in Biology or Chemistry are also required for Ph.D. applicants. For applications to the M.D.-Ph.D. program, the results of the Medical College Admission Test are accepted in lieu of the Graduate Record Examination.

Course Requirements In the first two years students are expected to complete a core curriculum that may include: Graduate Biochemistry, Cell Biology, Physiology, Neuroscience, Graduate Pharmacology, Molecular Pharmacology, Molecular Biology, Immunology, and Graduate Seminar.

Minor Requirements and Laboratory Rotations Students are required to rotate through two or three laboratories. Until the student selects a major sponsor, the Curriculum Committee will supervise the student's graduate program. The minor requirements must be completed before the student can take the Admission to Candidacy Examination.

Admission to Doctoral Candidacy The Admission to Candidacy Examination consists of two parts: a uniform written exam and an oral defense of a written research proposal. It is expected that most students will take this exam by the end of their second year.

Special Committee A student's Special Committee will be chosen by the student and major sponsor in consultation with the Curriculum Committee after the student chooses a major sponsor for thesis research.

Courses

General Pharmacology This basic pharmacology course consists of lectures, demonstrations, and small group conferences. The purpose of these exercises is to teach the principles of pharmacology to second-year medical students and to graduate students. Detailed consideration is given to the parameters of drug action to provide the student with the fundamental concepts essential for the evaluation of any drug. Consequently, the scientific basis of pharmacology is emphasized. Prototype drugs, essentially considered systemically, serve to illustrate several mechanisms and parameters of drug action. Therapeutic applications are considered insofar as they illustrate principles of pharmacology or drug hazards. Second and third quarters, annually. Dr. Chan and staff.

Molecular Pharmacology Fundamental principles and mechanisms governing the effects of chemicals on living systems are examined from the viewpoint of drug-cell interactions. Several theoretical concepts are introduced including drug selectivity, dose-response relationships, and fundamental mechanisms of drug actions. Also discussed are factors that govern the fate and time course of drugs in organisms including: drug absorption, distribution, biotransformation, pharmacokinetics. Examples of receptor isolation, drug-receptor interactions, and effector coupling are also examined. Not offered 1987–88.

Neuropharmacology This course presents the neuropharmacology of selected drugs and chemical substances that affect the central nervous system. Emphasis is placed on molecular mechanisms of drug actions with regard to the biochemistry and physiology of nervous tissue. These considerations include mechanisms of neurotransmitter actions, including drug actions that modify neurotransmitter actions. Several pharmacologic concepts important to understanding drug action on the nervous system are considered throughout. These include selectivity, specificity dose-response and receptor theory. Offered 1987–88, third quarter. Dr. Okamoto and staff.

Other Academic Offerings

Research in Pharmacology Research opportunities may be arranged throughout the year for graduate students who are not majoring in pharmacology but who want some investigative experience in the discipline. Special opportunities are offered for work on the nervous and cardiovascular systems and in biochemical and clinical aspects of pharmacology.

Seminars The Pharmacology Program offers seminars in areas of interest to its faculty and graduate students. Seminars in clinical pharmacology and teaching rounds are held regularly throughout the year. The content, format and schedule of these seminars are determined each year on the basis of the number and backgrounds of the interested students.

Journal Clubs These are offered in areas of pharmacology of special interest. Topics include the role of oxytocin and prostaglandin in labor and dysmenorrhea; regulation of opioid peptide biosynthesis; cardiovascular pharmacology of anaphylactic responses; neuropharmacology of drugs of abuse; clinical and geriatric pharmacology; clinical drug studies in the pediatric population; and prostaglandin and leukotriene pharmacology, their action on cardiovascular and renal systems. Each topic is one quarter in length; see the Program Directors for further information.

Physiology and Biophysics

Graduate Program Chairman

Erich E. Windhager, Department of Physiology and Biophysics, Room C-508, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, (212) 472-5229

Graduate Program Director

Thomas Maack, Department of Physiology and Biophysics, Room D-407, Cornell University Medical College, 1300 York Avenue, New York, NY 10021, (212) 472-5281

Opportunities are offered toward the Ph.D. degree in several areas of physiology and biophysics. Ample space is available, and laboratories are well equipped to provide predoctoral training in a medical environment. Interested individuals are urged to contact the Program Chairman before preparing a formal application. Letters of inquiry should include a discussion of the educational background and indicate possible areas of emphasis in graduate study. There has been a tendency to encourage applications from individuals who have a probable interest in more than one of the areas of physiology represented within the program.

Applicants must have completed introductory courses in biology, inorganic and organic chemistry, physics, and mathematics through the level of differential and integral calculus. Additional course work in these disciplines at the undergraduate level is encouraged. Applicants with otherwise exemplary records who lack certain course requirements will be considered for acceptance provided that they remedy their deficiencies while in training.

The course of study emphasizes the importance of teaching and research in the preparation and development of individuals for careers in physiology. This goal is achieved by a combination of didactic courses, seminars, and closely supervised research leading toward the preparation of a satisfactory thesis.

A special program of study will be developed for each student in consultation with

his or her Special Committee. In addition to the general requirements set by the Graduate School for all programs, all candidates for the doctoral degree in physiology will be expected to meet the following requirements:

1. Evidence of a satisfactory background in neurosciences. Ordinarily, the course in neuroscience described under the Program in Neurobiology and Behavior, or an equivalent course, will be taken concurrently with the course in physiology and biophysics.
2. Satisfactory completion of the course in physiology and biophysics, or an equivalent course.
3. For majors and minors in the program, a minimum of two elective courses in the program ordinarily will be required, in addition to the course in Physiology and Biophysics.

Courses

Physiology and Biophysics Lectures and conferences on body fluids, bioelectric phenomena, endocrinology and circulation. Third quarter, annually. Dr. Windhager and staff. Endocrinology is taught as an interdisciplinary course during two weeks of this quarter using hours normally allocated to courses in physiology, cell biology, and biochemistry (course coordinator: Dr. Greif).

Lectures and conferences on respiration, kidney function, acid-base regulation, and gastrointestinal function; and a weekly laboratory on selected aspects of physiology. Fourth quarter, annually. Dr. Windhager and staff.

Topics in Membrane Physiology This weekly conference is designed for Ph.D. and M.D.-Ph.D. students with a major or minor in Physiology and Biophysics. It is at a somewhat advanced level, especially in its quantitative approach to physiology. The aims of the conference are to train students in physiological concepts, to facilitate the understanding of lecture material in the Physiology and Biophysics course, and to establish close student-faculty contact. Third quarter, annually. Dr. Andersen.

Selected Topics in Kidney and Electrolyte Physiology and Pathophysiology Lectures, seminars and demonstrations. Topics include: 1) GFR, clearance concept, reabsorption and secretion of electrolytes; 2) concentrating mechanism; 3) electrophysiology of the nephron; 4) pathophysiology of potassium; 5) renal blood flow and its intrarenal distribution; 6) renal physiology in the newborn; 7) control of body fluid volume and tonicity; 8) pathology and pathophysiology of renal failure; urinary sediment; 9) radiology of the kidneys; 10) dialysis; 11) transplantation. Minimum of 8 students. Fourth quarter, annually. Drs. Maack, Windhager and staff.

Ionic Channels The course covers mathematical and experimental approaches to the topic of ion movement through single channels. Minimum of 5 students. Prerequisite: 2 years of calculus. Fourth quarter, annually. Dr. Andersen and invited lecturers.

Physiology of Cardiac Muscle The course is designed to present cellular mechanisms which are involved in the fundamental processes of excitation and contraction of cardiac muscle. Topics include: 1) action potential; 2) ion transport; 3) contractility (positive and negative inotropic effects); 4) excitation-contraction coupling; 5) arrhythmias; 6) cardiac failure. One laboratory day is planned for demonstrations of changes in action potential and twitch tension by inotropic agents. Minimum of 5 students. Prerequisites: third quarter physiology or equivalent. Fourth quarter, annually. Dr. Lee and invited lecturers.

Topics in Gastrointestinal Physiology Lectures and Seminars. Topics include: 1) functional morphology of stomach and intestine; 2) proliferation and differentiation of gastrointestinal cells; 3) motility of swell in esophagus, small intestine and colon; 4) gastric and intestinal secretion; pancreatic secretion; 5) lipid absorption; 6) intestinal absorption of calcium and vitamin D; 7) structure and function of bile acids; 8) gastrointestinal hormones. Minimum: 8 students. Fourth quarter, annually. Dr. Lipkin and invited experts in the field.

Register

University Administration

Frank H. T. Rhodes, President of the University

Robert Barker, University Provost

Thomas H. Meikle, Jr., Provost for Medical Affairs and Dean of the Medical College

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William D. Gurowitz, Vice President for Campus Affairs

Robert M. Matyas, Vice President for Facilities and Business Operations

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James A. Sanderson, Chief Investment Officer

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Walter J. Relihan, Jr., University Counsel and Secretary of the Corporation

Graduate School of Medical Sciences

Administration

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Alison P. Casarett, Dean of the Graduate School

Bernard L. Horecker, Dean of the Graduate School of Medical Sciences, Associate Dean of the Graduate School

Dieter H. Sussdorf, Associate Dean of the Graduate School of Medical Sciences, Assistant Dean of the Graduate School

Richard A. Rifkind, Director, Sloan-Kettering Division

Standing Committees

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Osias Stutman

Erich E. Windhager

Faculty Advisory Committee

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Curriculum Committee

Donald A. Fischman, Chair

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Bo DuPont

*nonvoting member

Alton Meister
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Erich E. Windhager

Credentials Review Committee

Dieter H. Sussdorf, Chair
Rosemary F. Bachvarova
Robert W. Knowles
Joel D. Pardee
Martin Sonenberg

M.D.-Ph.D. Program Committee

Donald A. Fischman, Chair
Kenneth I. Berns
Marvin C. Gershengorn
Jerard Hurwitz
Ralph L. Nachman
Osias Stutman

Committee on Student Prizes

Michiko Okamoto, Chair
David P. Hajjar
Kenneth O. Lloyd
Joel D. Pardee

Faculty

Albino, Anthony P., Assistant Professor of Immunology. B.A. 1970, Hunter College; Ph.D. 1974, Cornell University

Alonso, Daniel R., Professor of Pathology. M.D. 1962, University of Cuyo (Argentina)

Andersen, Olaf S., Professor of Physiology and Biophysics. Candidatus Medicinae 1971, University of Copenhagen (Denmark)

Bachvarova, Rosemary F., Associate Professor of Cell Biology and Anatomy. B.A. 1961, Radcliffe College; Ph.D., 1966, Rockefeller University

Bader, David M., Assistant Professor of Cell Biology and Anatomy. B.A. 1974, Augustana College; Ph.D. 1978, University of North Dakota

Baker, Harriet D., Associate Research Professor of Neurology. B.A. 1963, Wells College; M.S. 1967, University of Illinois; Ph.D. 1976, University of Iowa

Bank, Arthur, Adjunct Professor of Cell Biology and Anatomy. B.A. 1956, Columbia University; M.D. 1960, Harvard University Medical School

Barany, Francis, Assistant Professor of Microbiology. B.A. 1976, University of Illinois at Chicago Circle; Ph.D. 1981, Rockefeller University

Becker, Carl G., Professor of Pathology. B.S. 1957, Yale University; M.D. 1961, Cornell University

Bedford, J. Michael, Professor of Cell Biology and Anatomy. B.A. 1955, M.A., V.M.D. 1958, Cambridge University (England); Ph.D. 1965, University of London (England)

Berns, Kenneth I., R.A. Rees Pritchett Professor of Microbiology. A.B. 1960, Ph.D. 1964, M.D. 1966, Johns Hopkins University

Bertino, Joseph R., Professor of Developmental Therapy and Clinical Investigation. B.S. 1950, Cornell University; M.D. 1954, Downstate Medical Center

Besmer, Peter, Assistant Professor of Molecular Biology. M.S. 1964; Ph.D. 1969, Eidgenössische Technische Hochschule (Switzerland)

Bianco, Celso, Adjunct Professor of Cell Biology and Anatomy. M.D. 1966, Escola Paulista de Medicina (Sao Paulo, Brazil)

Biedler, June L., Professor of Cell Biology and Genetics. A.B. 1947, Vassar College; Ph.D. 1959, Cornell University

Bigler, Rodney E., Associate Professor of Physiology and Biophysics. B.S. 1966, Portland State College; Ph.D. 1971, University of Texas

Black, Ira B., Nathan Cummings Professor of Neurology. A.B. 1961, Columbia College; M.D. 1965, Harvard University

Blass, John P., Winifred Masterson Burke Professor of Neurology. Professor of Medicine. A.B. 1958, Harvard University; Ph.D. 1960, University of London (England), M.D. 1965, Columbia University

Bockman, Richard Steven, Associate Professor of Medicine. B.A. 1962, Johns Hopkins University; M.D. 1967, Yale University School of Medicine; Ph.D. 1971, Rockefeller University

Boskey, Adele L., Professor of Biochemistry. B.A. 1964, Barnard College; Ph.D. 1970, Brown University

Boyse, Edward A., Professor of Immunology. M.B.B.S. 1952, M.D. 1957, University of London (England)

Breslow, Esther M., Professor of Biochemistry. B.S. 1953, Cornell University; M.S. 1955, Ph.D. 1959, New York University

Brooks, Dana C., Professor of Cell Biology and Anatomy. B.E.E. 1949, M.D. 1957, Cornell University

Bullough, Peter, Professor of Pathology. M.D. 1956, Liverpool University (England)

Cayre, Yvon, Assistant Professor of Immunology. M.D. 1972, Montpellier Faculty of Medicine (France); Dr. Sci. 1978, Paris Faculty of Science (France)

Chaganti, Raju S., Associate Professor of Cell Biology and Genetics. B.S. 1954, M.S. 1955, Andhra University (India); Ph.D. 1964, Harvard University

Chan, Walter W. Y., Professor of Pharmacology. B.A. 1956, University of Wisconsin; Ph.D. 1961, Columbia University

Chao, Moses V., Assistant Professor of Cell Biology and Anatomy. B.A. 1973, Pomona College; Ph.D. 1980, University of California at Los Angeles

Chou, Ting-Chao, Associate Professor of Developmental Therapy and Clinical Investigation. B.S. 1961, Kaohsiung Medical College (Taiwan); M.S. 1965, National Taiwan University; Ph.D. 1970, Yale University

Cooper, Arthur J. L., Associate Research Professor of Biochemistry in Neurology, Assistant Professor of Biochemistry. B.Sc. 1967, M.Sc. 1969, University of London (England); Ph.D. 1974, Cornell University

Darzynkiewicz, Zbigniew, Associate Professor of Cell Biology and Genetics. M.D. 1960, Academy of Medicine, Warsaw (Poland); Ph.D. 1965, Academy of Medicine and Polish Academy of Sciences (Poland)

Dickerman, Robert W., Associate Professor of Microbiology. B.S. 1951, Cornell University; M.A. 1953, University of Arizona; Ph.D. 1961, University of Minnesota

Donner, David B., Associate Professor of Cell Biology and Genetics. B.A. 1966, Queens College; Ph.D. 1972, Rensselaer Polytechnic Institute

Dreyfus, Cheryl F., Assistant Research Professor of Developmental Neurology in Neurology. Assistant Professor of Cell Biology and Anatomy. B.S. 1967, University of Vermont; M.S. 1969, Ph.D. 1976, Cornell University

Dupont, Bo, Professor of Immunology. M.D. 1966, University of Arhus (Denmark)

Edelson, Paul, Associate Professor of Pediatrics in Microbiology. A.B. 1964, University of Rochester; M.D. 1969, State University of New York, Downstate Medical Center, Brooklyn, New York

Eisinger, Magdalena G., Associate Professor of Cell Biology and Genetics. D.V.M. 1962, Agricultural University Kosice (Czechoslovakia)

Ellis, John T., David D. Thompson Professor of Pathology. B.A. 1942, University of Texas; M.D. 1945, Northwestern University

Fairclough, Gordon F., Associate Professor of Biochemistry. B.A. 1960, Ph.D. 1966, Yale University

Falck-Pedersen, Erik, Assistant Professor of Microbiology. B.A. 1976, North Central College; Ph.D. 1982, University of Illinois

Fell, Colin, Associate Professor of Physiology and Biophysics. B.A. 1951, Antioch College; M.S. 1953, Ph.D. 1957, Wayne State University

Felsen, Diane F., Assistant Professor of Pharmacology in Surgery. B.A. 1974, Queens College; Ph.D. 1979, Mt. Sinai School of Medicine

Fischman, Donald A., Harvey Klein Professor of Biomedical Sciences in Cell Biology and Anatomy. A.B. 1957, Kenyon College; M.D. 1961, Cornell University

Flomenberg, Neal, Assistant Professor of Immunology. B.S. 1974, Pennsylvania State University; M.D. 1976, Jefferson Medical College

Fox, Jack J., Professor of Developmental Therapy and Clinical Investigation. A.B. 1939, Ph.D. 1950, University of Colorado

Fried, Jerrold, Associate Professor of Developmental Therapy and Clinical Investigation. B.S. 1958, California Institute of Technology; Ph.D. 1964, Stanford University

Gardner, Daniel, Associate Professor of Physiology and Biophysics. A.B. 1966, Columbia College; Ph.D. 1971, New York University

Gass, Jerald D., Associate Professor of Biochemistry. B.S. 1957, University of Oklahoma; A.M. 1962, Harvard University; Ph.D. 1969, Cornell University

Gazzaniga, Michael S., Professor of Neuropsychology in Neurology. A.B. 1961, Dartmouth College; Ph.D. 1964, California Institute of Technology

Gelbard, Allan S., Associate Professor of Developmental Therapy and Clinical Investigation. B.S. 1955, Brooklyn College; M.S. 1956, University of Massachusetts; Ph.D. 1959, University of Wisconsin

Geller, Nancy L., Assistant Professor of Developmental Therapy and Clinical Investigation. B.S. 1965, City University of New York; M.A. 1967, Case Institute of Technology; Ph.D. 1972, Case Western Reserve University

German, James L. III, Clinical Professor of Pediatrics. B.S. 1945, Louisiana Polytechnic Institute; M.D. 1949, Southwestern Medical College

Gershengorn, Marvin C., Abbey Rockefeller Mauzé Distinguished Professor of Endocrinology in Medicine. Professor of Medicine in Physiology and Biophysics. B.S. 1967, City College of the City University of New York; M.D. 1971, New York University School of Medicine

Gibbs, James G. Jr., Associate Professor of Psychiatry. B.S. 1960, Trinity College; M.D. 1964, Medical College of South Carolina

Gibson, Gary E., Associate Professor of Biochemistry in Neurology. B.S. 1968, University of Wyoming; Ph.D. 1973, Cornell University

Gilboa, Eli, Associate Professor of Molecular Biology. B.Sc. 1971, M.Sc. 1973, Hebrew University, Jerusalem; Ph.D. 1977, Weizmann Institute of Science.

Gilder, Helena, Adjunct Associate Professor of Biochemistry. Adjunct Associate Professor of Pediatrics. A.B. 1935, Vassar College; M.D. 1940, Cornell University

Goldstein, Jack, Adjunct Associate Professor of Biochemistry. B.A. 1952, Brooklyn College; M.N.S. 1957, Ph.D. 1959, Cornell University

Graf, Lloyd H. Jr., Adjunct Assistant Professor of Genetics in Obstetrics and Gynecology. B.S. 1967, Ph.D. 1972, Duke University

Grafstein, Bernice, Vincent and Brook Astor Distinguished Professor of Neuroscience in Physiology and Biophysics. B.A. 1951, University of Toronto (Canada); Ph.D. 1954, McGill University (Canada)

Greif, Roger L., Emeritus Professor of Physiology and Biophysics. B.S. 1937, Haverford College; M.D. 1941, Johns Hopkins University

Griffith, Owen W., Associate Professor of Biochemistry. B.A. 1968, University of California at Berkeley; Ph.D. 1976, Rockefeller University

Hajjar, David P., Associate Professor of Pathology. Associate Professor of Biochemistry. B.A. 1974, American International College; M.S. 1977, Ph.D. 1978, University of New Hampshire

Halmi, Katherine A., Professor of Psychiatry. B.A. 1961, M.D. 1965, University of Iowa

Hammerling, Ulrich, Professor of Immunology. Diplom 1961 Universität Freiburg (Germany); Ph.D. 1965, Max Planck Institut für Immunobiologie (Germany)

Haschemeyer, Rudy H., Professor of Biochemistry. B.A. 1952, Carthage College; Ph.D. 1957, University of Illinois

Hayward, William S., Professor of Molecular Biology. B.A. 1964, University of California, Riverside; Ph.D. 1969, University of California, San Diego

Hinkle, Lawrence E. Jr., Professor of Medicine; Professor of Medicine in Psychiatry. B.A. 1938, University of North Carolina; M.D. 1942, Harvard University

Hoffmann, Michael K., Associate Professor of Immunology. M.D. 1966, Universität Tübingen (Germany)

Holloman, William, Professor of Microbiology. B.S. 1967, University of Texas; Ph.D. 1971, University of California, Berkeley

Horecker, Bernard L., Dean, Professor of Biochemistry. B.S. 1936, Ph.D. 1939, University of Chicago

Hosein, Barbara H., Adjunct Assistant Professor of Cell Biology and Anatomy. B.A. 1969, University of Kansas; M.S. 1971, Ph.D. 1973, University of Michigan

Houghton, Alan, Assistant Professor of Immunology. B.A. 1970, Stanford University; M.D. 1974, University of Connecticut

Hurwitz, Jerard, Professor of Molecular Biology. B.A. 1949, Indiana University; Ph.D. 1953, Western Reserve University

Hutchison, Dorris J., Professor of Cell Biology and Genetics. B.S. 1940, Western Kentucky State College; M.S. 1943, University of Kentucky; Ph.D. 1949, Rutgers University

Iacovitti, Lorraine, Assistant Professor of Neurobiology in Neurology. B.S. 1973, Monmouth College; Ph.D. 1979, Cornell University Graduate School of Medical Sciences

Inturrisi, Charles E., Professor of Pharmacology. B.S. 1962, University of Connecticut; M.S. 1965, Ph.D. 1967, Tulane University

Jacobs, Patricia A., Professor of Genetics in Pediatrics. Professor of Genetics in Obstetrics and Gynecology. B.Sc. 1956, D.Sc. 1966, St. Andrews University (Scotland)

Jack, Joseph R., Assistant Professor of Molecular Biology. B.A. 1972, Vanderbilt University; Ph.D. 1978, University of Texas

Jaffe, Eric, Professor of Medicine. M.D. 1966, State University of New York, Downstate Medical Center

Joh, Tong Hyub, Professor of Neurobiology in Neurology. B.S. 1953, Seoul National University (Korea); Ph.D. 1971, New York University

Keithly, Jan S., Assistant Professor of Microbiology; Assistant Professor of Microbiology in Medicine. B.S. 1963, Central Missouri State University; Ph.D. Iowa State University

King, Thomas K. C., Associate Professor of Medicine, Associate Professor of Medicine in Physiology and Biophysics. M.B.B.Ch. 1959, M.D. 1963, University of Edinburgh (United Kingdom)

Klein, Irwin L., Associate Professor of Medicine. B.A. 1969, University of Pennsylvania; M.D. 1973, New York University School of Medicine

Knowles, Robert, Assistant Professor of Immunology. A.B. 1970, Bowdoin College; Ph.D. 1976, Pennsylvania State University

Kourides, Ione A., Associate Professor of Cell Biology and Genetics. B.A. 1963, Wellesley College; M.D. 1967, Harvard University

Krug, Robert M., Professor of Molecular Biology. B.A. 1961, Harvard University; Ph.D. 1966, Rockefeller University

Lacy, Elizabeth, Assistant Professor of Molecular Biology. B.A. 1974, University of Pennsylvania; Ph.D. 1980, California Institute of Technology

Lai, Chun-Yen, Adjunct Professor of Biochemistry. B.S. 1953, M.S. 1957, National Taiwan University; Ph.D. 1961, University of Illinois

Laughlin, John S., Professor of Developmental Therapy and Clinical Investigation. A.B. 1940, Willamette University; Ph.D. 1947, University of Illinois

LeDoux, Joseph E., Assistant Professor of Neurology. B.S. 1971, M.S. 1974, Louisiana State University; Ph.D. 1977, State University of New York at Stony Brook

Lee, Chin Ok, Professor of Physiology and Biophysics. M.S. 1967, Seoul National University (Korea); Ph.D. 1973, Indiana University School of Medicine

Lee, Janet, Assistant Professor of Immunology. B.A. 1972, University of Minnesota; M.S. 1974, University of Wisconsin; Ph.D. 1979, University of California at San Francisco

Levi, Roberto, Professor of Pharmacology. M.D. 1960, University of Florence (Italy)

Levy, David E., Associate Professor of Neurology. A.B. 1963, M.D. 1968, Harvard University

Lin, Chiann-Tso, Assistant Professor of Physiology and Biophysics. Diploma of Engineering 1963, Taipei Institute of Technology; Diploma of Chemistry (Master) 1970, Technical University of Braunschweig (West Germany); Ph.D. 1974, University of Frankfurt (West Germany)

Lipkin, Martin, Professor of Medicine. A.B. 1946, M.D. 1950, New York University

Lloyd, Kenneth O., Associate Professor of Immunology. Ph.D. 1960, University of College of North Wales (U.K.)

Lockard, Raymond E., Assistant Professor of Biochemistry. B.S. 1966, Syracuse University; Ph.D. 1972, University of Cincinnati

Lustig, Arthur J., Assistant Professor of Molecular Biology. B.A. 1975, Ph.D. 1981, The University of Chicago

Maack, Thomas, Professor of Physiology and Biophysics. M.D. 1962, University of Sao Paulo (Brazil)

Mann, J. John, Associate Professor of Psychiatry. B.S., M.D. 1971, University of Melbourne (Australia)

Marians, Kenneth J., Associate Professor of Molecular Biology. B.S. 1972, Polytechnic Institute of Brooklyn; Ph.D. 1976, Cornell University

Marks, Paul A., Professor of Cell Biology and Genetics. A.B. 1945, Columbia University; M.D. 1949, College of Physicians and Surgeons, Columbia University

Meister, Alton, Israel Rogosin Professor of Biochemistry. B.S. 1942, Harvard University; M.D. 1945, Cornell University

Melamed, Myron R., Professor of Cell Biology and Genetics. B.S. 1947, Western Reserve University; M.D. 1950, University of Cincinnati

Melera, Peter W., Assistant Professor of Molecular Biology. A.A.S. 1963, State University of New York at Cobleskill; B.S.A. 1965, Ph.D. 1969, University of Georgia

Minick, C. Richard, Professor of Pathology. B.S. 1957, University of Wyoming; M.D. 1960, Cornell University

Montal, Mauricio, Adjunct Professor of Pharmacology. Ph.D. 1970, University of Pennsylvania; M.D. 1971, National University of Mexico

Moore, Malcolm A. S., Professor of Cell Biology and Genetics. M.B. 1963, B.A. 1964, D. Phil. 1967, M.A. 1970, Oxford University (England)

Morton, Newton E., Professor of Cell Biology and Genetics. B.A. 1951, University of Hawaii; M.S. 1952, Ph.D. 1955, University of Wisconsin

Muller-Eberhard, Ursula, Professor of Pediatrics; Professor of Pharmacology. M.D. 1953, University of Göttingen (Germany)

Murray, Henry W., Associate Professor of Microbiology. B.A. 1968, Cornell University; M.D. 1972, Cornell University Medical College

Nachman, Ralph L., Professor of Medicine. A.B. 1953, M.D. 1956, Vanderbilt University

Nathan, Carl, Stanton Griffis Distinguished Professor of Medicine. B.A. 1967, Harvard University; M.D. 1972, Harvard Medical School.

Neff, Norma, Assistant Professor of Molecular Biology. B.A. 1974, Rice University; Ph.D. 1978, University of California, Berkeley

Novogrodsky, Abraham, Professor of Biochemistry. M.D. 1960, Hebrew University Medical School, Jerusalem; Ph.D. 1974, Weizmann Institute of Science, Rehovot (Israel)

O'Donnell, Michael E., Assistant Professor of Microbiology. B.S. 1975, University of Portland; Ph.D. 1982, University of Michigan

O'Donnell, Paul V., Associate Professor of Molecular Biology. B.S. 1968, Rensselaer Polytechnic Institute; Ph.D. 1973, Cornell University

Oettgen, Herbert F., Professor of Immunology. M.D. 1951, University of Cologne (Germany)

Okamoto, Michiko, Professor of Pharmacology. B.S. 1954, Tokyo College of Pharmacy (Japan); M.S. 1957, Purdue University; Ph.D. 1964, Cornell University

Old, Lloyd J., Professor of Immunology. B.A. 1955, M.D. 1958, University of California

O'Leary, William M., Professor of Microbiology. B.S. 1952, M.S. 1953, Ph.D. 1957, University of Pittsburgh

O'Reilly, Richard J., Professor of Immunology. A.B. 1964, College of the Holy Cross; M.D. 1968, University of Rochester

Osley, Mary Ann, Assistant Professor of Molecular Biology. B.A. 1967, Wheaton College; Ph.D. 1973, Yale University

Otter, Brian A., Associate Professor of Developmental Therapy and Clinical Investigation. B.Sc. 1962, Ph.D. 1965, University of Bristol (England)

Palmer, Lawrence G., Associate Professor of Physiology and Biophysics. B.A. 1970, Swarthmore College; Ph.D. 1976, University of Pennsylvania

Pardee, Joel D., Assistant Professor of Cell Biology and Anatomy. B.S. 1973, Colorado State University; Ph.D. 1978, Stanford University

Pasternak, Gavril W., Associate Professor of Pharmacology. B.A. 1969, M.D. 1973, Ph.D. 1974, Johns Hopkins University

Pelus, Louis M., Assistant Professor of Cell Biology and Genetics. B.A. 1973, Queens College of the City University of New York; M.S. 1977, Ph.D. 1977, Rutgers University

Pasternak, Gavril W., Associate Professor of Neurology. Associate Professor of Pharmacology. B.A. 1969, M.D. 1973, Ph.D. 1974, Johns Hopkins University

Pelus, Louis M., Assistant Professor of Cell Biology and Genetics. B.A. 1973, Queens College of the City University of New York; M.S. 1977, Ph.D. 1977, Rutgers University

Petito, Carol K., Professor of Pathology. B.S. 1963, Jackson College; M.D. 1967, Columbia University

Pickel, Virginia M., Professor of Neurobiology in Neurology. B.S. 1965, M.S. 1967, University of Tennessee; Ph.D. 1970, Vanderbilt University

Pickering, Thomas G., Professor of Medicine. B.A. 1962, M.A. 1968, Cambridge University (England); Ph.D. 1970, Oxford University (England)

Plum, Fred, Anne Parrish Titzell Professor of Neurology. B.A. 1944, Dartmouth College; M.D. 1947, Cornell University

Prince, Alfred M., Clinical Associate Professor of Pathology. A.B. 1949, Yale University; M.A. 1951, Columbia University; M.D. 1955, Western Reserve University

Quimby, Fred, Associate Professor of Pathology. V.D.M. 1970, University of Pennsylvania School of Veterinary Medicine; Ph.D. 1974, University of Pennsylvania Graduate School of Arts and Sciences

Rabellino, Enrique M., Senior Research Associate Professor of Medicine. B.S. 1959, Institute J. M. Paz (Argentina); M.D. 1965, University of Cordoba (Argentina)

Rabkin, Samuel D., Assistant Professor of Molecular Biology. B.Sc. 1976, University of Toronto; M.Sc. 1978, Hebrew University of Jerusalem; Ph.D. 1983, University of Chicago

Rachele, Julian R., Emeritus Professor of Biochemistry. B.A. 1934, M.S. 1935, Ph.D. 1939, New York University

Ravetch, Jeffrey A., Associate Professor of Molecular Biology. B.S. 1973, Yale University; Ph.D. 1978, Rockefeller University; M.D. 1979, Cornell University

Ray, James H., Adjunct Assistant Professor of Cell Biology and Anatomy. B.A. 1967, Murray State University; M.S. 1969, University of Kentucky, Ph.D. 1976, University of Houston

Rayson, Barbara, Assistant Professor of Physiology and Biophysics; Assistant Professor of Medicine in Physiology. B.Sc. 1972, Ph.D. 1976, University of Melbourne (Australia)

Reeves, John P., Adjunct Associate Professor of Physiology and Biophysics. B.S. 1964, Juniata College; Ph.D. 1969, Massachusetts Institute of Technology

Reidenberg, Marcus M., Professor of Pharmacology. B.S. 1954, Cornell University; M.D. 1958, Temple University

Reis, Donald J., George C. Cotzias Distinguished Professor of Neurology. A.B. 1953, M.D. 1956, Cornell University

Rifkind, Arleen B., Professor of Pharmacology; Associate Professor of Medicine. B.A. 1960, Bryn Mawr College; M.D. 1964, New York University

Rifkind, Richard A., Professor of Cell Biology and Genetics. B.S. 1951, Yale University; M.D. 1955, Columbia University

Riker, Walter F. Jr., Revlon Pharmaceutical Emeritus Professor of Pharmacology. B.S. 1939, Columbia University; M.D. 1943, Cornell University

Rodman, Toby C., Professor of Cell Biology and Anatomy. B.S. 1937, Philadelphia College of Pharmacy and Science; M.S. 1961, Ph.D. 1963, New York University

Rodriguez-Bouland, Enrique, Associate Professor of Cell Biology and Anatomy. B.A. 1963, National College of Buenos Aires; M.D. 1970, University of Buenos Aires (Argentina)

Rosen, Ora M., Professor of Molecular Biology. B.A. 1956, Barnard College; M.D. 1960, Columbia University

Rothermel, Constance Davis, Assistant Professor of Microbiology. B.S. 1964, West Virginia University; M.S. 1967, University of North Carolina; Ph.D. 1980, Cornell University Graduate School of Medical Sciences

Rottenberg, David A., Associate Professor of Neurology. B.A. 1963, University of Michigan; M.Sc. 1967, University of Cambridge (England); M.D. 1969, Harvard University

Rubin, Albert L., Professor of Biochemistry. Professor of Surgery. Professor of Medicine. M.D. 1950, Cornell University

Ruggiero, David A., Assistant Professor of Neurobiology in Neurology. B.A. 1972, Queens College of the City University of New York; M.A. 1976, M. Phil. 1977, Ph.D. 1977, Columbia University

Safai, Bijan, Assistant Professor of Immunology. M.D. 1965, University of Teheran Medical School (Iran)

Santos-Buch, Charles A., Professor of Pathology. A.B. 1953, Harvard University; M.D. 1957, Cornell University

Saxena, Brij B., Professor of Endocrinology in Obstetrics and Gynecology. Ph.D. 1954, University of Lucknow (India); D.Sc. 1957, University of Münster (Germany); Ph.D. 1961, University of Wisconsin

Schleifer, Leonard S., Assistant Professor of Neurology. A.B. 1973, Cornell University; M.D. 1977, University of Virginia School of Medicine; Ph.D. 1980, University of Virginia

Schubert, Edward T., Assistant Professor of Biochemistry in Pediatrics. B.S. 1949, M.S. 1952, Ph.D. 1959, Fordham University

Schwartz, Morton K., Professor of Developmental Therapy and Clinical Investigation. B.A. 1948, Lehigh University; Ph.D. 1952, Boston University

Sechzer, Jeri A., Associate Professor of Psychology in Psychiatry. B.S. 1956, New York University; M.A. 1961, Ph.D. 1962, University of Pennsylvania

Sen, Ganes C., Associate Professor of Molecular Biology. B.S. 1965, M.S. 1967, Calcutta University (India); Ph.D. 1974, McMaster University (Canada)

Senterfit, Laurence B., Professor of Microbiology. Professor of Pathology. B.S. 1949, M.S. 1950, University of Florida; Sc.D. 1955, Johns Hopkins University

Shapiro, Joan Rankin, Assistant Professor of Cell Biology in Neurology. B.S. 1960, Westminster College; M.S. 1968, New York University; M.A. 1970, Hofstra University; Ph.D. 1979, Cornell University

Sheffery, Michael, Assistant Professor of Molecular Biology. A.B. 1975, M.S. 1977, Ph.D. 1981, Princeton University

Sherline, Peter, Associate Professor of Medicine. A.B. and M.D. 1968, Boston University Medical School

Silverstein, Roy L., Clinical Assistant Professor of Medicine. B.S. 1975, Brown University; M.D. 1979, Emory University School of Medicine

Siniscalco, Marcello, Professor of Cell Biology and Genetics. M.D. 1948, University of Naples (Italy)

Sirlin, Julio L., Professor of Cell Biology and Anatomy. D.Sc. 1953, University of Buenos Aires (Argentina)

Sirotnak, Francis M., Professor of Developmental Therapy and Clinical Investigation. B.S. 1950, University of Scranton; Ph.D. 1954, University of Maryland

Siskind, Gregory W., Professor of Medicine. B.A. 1955, Cornell University; M.D. 1959, New York University

Smith, Gerard P., Professor of Psychiatry (Behavioral Science). B.S. 1956, St. Joseph's College; M.D. 1960, University of Pennsylvania

Soffer, Richard L., Professor of Biochemistry. Professor of Medicine. B.A. 1954, Amherst College; M.D. 1958, Harvard University

Solnick, David, Assistant Professor of Molecular Biology. B.A. 1976, University of California, Santa Cruz; Ph.D. 1981, SUNY, Stony Brook

Sonenberg, Martin, Professor of Cell Biology and Genetics. B.S. 1941, University of Pennsylvania; M.D. 1944, Ph.D. 1952, New York University

Staiano-Coico, Lisa, Assistant Professor of Microbiology in Surgery. B.S. 1976, Brooklyn College; Ph.D. 1981, Cornell University Graduate School of Medical Sciences

Stenzel, Kurt H., Professor of Biochemistry. Professor of Surgery. Professor of Medicine. B.S. 1954, New York University; M.D. 1958, Cornell University

Stephenson, John L., Professor of Biomathematics in Physiology and Biophysics. B.A. 1943, Harvard University; M.D. 1949, University of Illinois

Sternberg, Stephen S., Professor of Developmental Therapy and Clinical Investigation. B.A. 1941, Colby College; M.D. 1944, New York University

Stokes, Peter E., Professor of Medicine. Professor of Psychiatry. B.S. 1958, Trinity College; M.D. 1952, Cornell University

Stutman, Osias, Professor of Immunology. B.A. 1950, Colegio Nacional Sarmiento (Argentina); M.D. 1957, Buenos Aires University Medical School (Argentina)

Sugg, John V., Emeritus Professor of Microbiology. A.B. 1926, M.S. 1928, Ph.D. 1931, Vanderbilt University

Sussdorf, Dieter H., Associate Dean, Associate Professor of Microbiology. B.A. 1952, University of Missouri; Ph.D. 1956, University of Chicago

Szabo, Paul, Assistant Professor of Molecular Biology in Medicine. B.S. 1971, Ph.D. 1974, University of Illinois

Szeto, Hazel H., Associate Professor of Pharmacology. B.S. 1972, Indiana University; Ph.D., M.D. 1977, Cornell University

Tate, Suresh S., Associate Professor of Biochemistry. B.Sc. 1958, M.Sc. 1960, University of Baroda (India); Ph.D. 1963, University of London (England)

Teintze, Martin, Assistant Professor of Cell Biology and Anatomy. B.S. 1976, California Institute of Technology; Ph.D. 1981, University of California

Teitelman, Gladys N., Associate Research Professor of Neurobiology in Neurology. Licendiada in Biology 1962, University of Buenos Aires (Argentina); Ph.D. 1971, University of Pennsylvania

Thaler, Howard T., Assistant Professor of Developmental Therapy and Clinical Investigation. B.A. 1967, University of California at Los Angeles; Ph.D. 1974, State University of New York at Buffalo

Townes-Anderson, Ellen, Assistant Professor of Physiology and Biophysics. B.A. 1968, Connecticut College; M.A. 1971, University of California at Berkeley; Ph.D. 1980, Boston University School of Medicine

Traktman, Paula, Assistant Professor of Cell Biology and Anatomy. Assistant Professor of Cell Biology and Anatomy in Microbiology. A.B. 1974, Radcliffe College, Harvard University; Ph.D. 1981, Massachusetts Institute of Technology

Udenfriend, Sidney, Adjunct Professor of Biochemistry. B.S. 1939, City College of New York; M.S. 1942, Ph.D. 1948, New York University

Urban, Bernd W., Assistant Professor of Anesthesiology. Assistant Professor of Anesthesiology in Physiology and Biophysics. Diplom der Physik (Master) 1974, University of Karlsruhe (West Germany); Ph.D. 1978, University of Cambridge (England)

Victor, Jonathan D., Associate Professor of Neurology. B.A. 1973, Harvard University; Ph.D. 1979, Rockefeller University; M.D. 1980, Cornell University Medical College

Wall, Doris A., Assistant Professor of Cell Biology and Anatomy. B.A. 1970, University of New Hampshire; Ph.D. 1975, Cornell University

Watanabe, Kyoichi A., Professor of Developmental Therapy and Clinical Investigation. Ph.D. 1963, Hokkaido University (Japan)

Weinstein, Alan M., Associate Professor of Physiology and Biophysics. Assistant Professor of Medicine. A.B. 1971, Princeton University; M.D. 1975, Harvard University

Weksler, Babette B., Professor of Medicine. B.A. 1958, Swarthmore College; M.D. 1963, Columbia University

Weksler, Marc E., Irving Sherwood Wright Professor of Geriatrics in Medicine. B.A. 1958, Swarthmore College; M.D. 1962, Columbia University

Wellner, Daniel, Associate Professor of Biochemistry. A.B. 1956, Harvard University; Ph.D. 1961, Tufts University

Windhager, Erich E., Maxwell M. Upson Professor of Physiology and Biophysics. M.D. 1954, University of Vienna (Austria)

Wong, George Y., Assistant Professor of Developmental Therapy and Clinical Investigation. B.A. 1973, Rice University; M.A. 1975, Ph.D. 1978, Harvard University

Woods, Kenneth R., Adjunct Associate Professor of Biochemistry. B.A. 1948, Arizona State University; Ph.D. 1955, University of Minnesota

Yang, Soo Young, Assistant Professor of Immunology. M.S. 1972, Minnesota State University; Ph.D. 1981, New York University

Young, Robert C., Associate Professor of Psychiatry in Neurobiology. B.A. 1969, Williams College; M.D. 1974, Cornell University

Zakim, David, Vincent Astor Distinguished Professor of Medicine. B.A. 1956, Cornell University; M.D. 1961, State University of New York Downstate Medical Center

Zeitz, Louis, Associate Professor of Developmental Therapy and Clinical Investigation. A.B. 1948, University of California; Ph.D. 1962, Stanford University

Degree Recipients 1986–87

Doctors of Philosophy

Askari, Frederick K., B.A. 1981, Cornell University. Pharmacology, Professor Walter Riker. Thesis: "Molecular Determinants of Carbamate Drug Action on Mammalian Neuromuscular Function"

Blank, Seymour G., B.E.E. 1965, City University of New York: M.E.E. 1968, New York University. Physiology and Biophysics, Professor Thomas G. Pickering. Thesis: "The Korotkoff Signal and Its Relationship to the Arterial Pressure Pulse"

Brennan, Lynn A., B.A. 1974, Rutgers University. Molecular Biology, Professor Edward Stavnezer. Thesis: "Molecular Cloning of the Viral Oncogene *V-SKI,* and Its Chicken Cellular Homolog, *C-SKI*"

Doucette, Lynn Anne, B.Sc. 1981, McMaster University (Canada). Cell Biology and Genetics, Professor Raju S. K. Chaganti. Thesis: "Molecular Analysis of t(14:18) Translocation in Non-Hodgkin's Lymphoma"

Green, William N., B.Sc. 1978, University of Toronto. Physiology and Biophysics, Professor Olaf S. Andersen. Thesis: "Studies of Batrachotoxin-Modified Sodium Channels in Planar Lipid Bilayers"

Hariri, Robert J., B.A. 1980, Columbia College. Pathology, Professor Daniel Alonso. Thesis: "The Role of Aging in the Development of Myointimal Hyperplasia Following Arterial Injury"

Levine, Sulamita, M.D. 1975, M.S. 1980, University of Zulia Medical School (Venezuela). Neurobiology and Behavior, Professor Tong H. Joh. Thesis: "Immunochemical and Immunocytochemical Characterization of Histidine Decarboxylase Prepared by a Rapid and Efficient Purification Procedure"

Lufkin, Thomas C., A.B. 1981, University of California, Berkeley. Molecular Biology, Professor E Carter Bancroft. Thesis: "Cis-Acting DNA Elements Responsible for the Cell-Type Specific Expression and Hormonal Regulation of the Prolactin and Growth Hormone Genes"

Michitsch, Richard W., B.A. 1975, M.S. 1978, New York University. Molecular Biology, Professor Peter Melera. Thesis: "Isolation and Characterization of the N-MYC Gene"

Shapiro, Geoffrey Ira, B.A. 1981, Columbia University. Molecular Biology, Professor Robert M. Krug. Thesis: "Influenza Virus Gene Expression: Viral Replication *in vivo* and *in vitro*"

Stinavage, Paul S., A.A.S. 1977, State University of New York at Morrisville: B.S. 1981, Marywood College. Microbiology, Professor Laurence B. Senterfit. Thesis: "The Role of Adrenal Hormones in the Hyperglycemic Response to Infection in Streptozotocin Diabetic C57BL/KsJ Mice"

Weisman, Steven M., B.S., B.A. 1981, Fairleigh Dickinson University. Pharmacology, Professor Diane Felsen. Thesis: "Involvement of Platelet-activating Factor in the Release of Prostaglandins in Unilateral Ureteral Obstruction"

Yang, Jung-Mou, M.B. 1979, National Defense Medical Center (People's Republic of China). Physiology and Biophysics, Professor Erich Windhager. Thesis: "Role of Intracellular Calcium Ions in Regulation of Na Transport"

Master of Science

Ark, Belinda Chan, A.B. 1984, Cornell University. Cell Biology and Genetics, Professor Dorothea Bennett. Thesis: "Mapping of the Pim-1 Oncogene to t-haplotypes in the Mouse"

Students 1987–88

Candidates for the Degree of Doctor of Philosophy

Abate, Corinne, B.A. 1983, Fordham University. Major: Neurobiology and Behavior. Brooklyn, New York

Ahn, Jong C., B.S. 1979, Seoul National University; M.S. 1981, Korea Advanced Institute of Science and Technology. Major: Molecular Biology. Gyounggido, Korea

Arnold, James B., B.A. 1982, Columbia College. Major: Neurobiology and Behavior. New York, New York

Bannerji, Rajat, B.A. 1986, Cornell University. Major: Cell Biology and Genetics. Durgapur, India

Barnhart, Kerry M., B.S. 1983, M.S. 1985, University of Arizona. Major: Molecular Biology. Tucson, Arizona

[1]Batter, David K., B.S. 1979, University of Connecticut. Major: Cell Biology and Genetics. New Haven, Connecticut

Bauchwitz, Robert P., B.A. 1982, Harvard University. Major: Molecular Biology. Wilmington, Delaware

Bayer, Virginia E., B.A./B.S. 1981, University of California. Major: Neurobiology and Behavior. Newport Beach, California

Becker, Murray, B.A. 1985, University of Chicago

Berger, Scott B., B.A. 1983, Emory University. Major: Neurobiology and Behavior. Pittsburgh, Pennsylvania

Bisaha, Joseph G., B.A. 1986, Rutgers University. Major: Cell Biology and Genetics. Perth Amboy, New Jersey

Blumenthal, Jeffrey A., B.A. 1985, Vassar College. Major: Immunology. Glenwood, Illinois

Brayton, Cory Flagg, B.A. 1981, Williams College; D.V.M. 1985, New York State College of Veterinary Medicine. Major: Microbiology, Immunology, and Pathology. New York, New York

Brock, Alice M., A.B. 1978, Smith College; M.S.H.S. 1980, Northeastern University. Major: Cell Biology and Genetics, Scarsdale, New York

Brooks, David G., B.A. 1982, University of Colorado; M.S. 1984, Michigan State University. Major: Cell Biology and Genetics. Rochester, Michigan

Buck, Charles R., B.S. 1983, College of Idaho. Major: Cell Biology and Genetics. Caldwell, Idaho

Chiu, Chang-Fang, M.D. 1980, Taipei Medical College. Major: Pharmacology. Taipei, Taiwan, Republic of China

[2]Choy, Janet Wing, A.B. 1977, Smith College. Major: Cell Biology and Genetics. Wayne, New Jersey

Clurman, Bruce E., B.A. 1981, University of Virginia. Major: Molecular Biology. Cherry Hill, New Jersey

Crombie, Andrea R., B.A. 1981, Goucher College. Major: Molecular Biology. San Diego, California

DeCarlo, Michele J., B.A. 1986, Lafayette College. Major: Molecular Biology. Philadelphia, Pennsylvania

del Balzo, Ughetta, B.A. 1981, Barnard College. Major: Pharmacology. Rome, Italy

Dieker, Adam P., B.A. 1984, Columbia University. Major: Cell Biology and Genetics. Great Neck, New York

DiSanto, James P., B.A. 1983, Johns Hopkins University. Major: Immunology. Cherry Hill, New Jersey

Donnelly, Robert E., B.S. 1985, University of California. Major: Biochemistry. Cupertino, California

[3]Drozdoff, Vladimir V., B.A. 1979, Bowdoin College. Major: Developmental Therapy and Clinical Investigation. Cooper, Maine

Einheber, Steven, B.S. 1981, George Washington University. Major: Cell Biology and Genetics. Washington, D.C.

[1]in absentia
[2]leave of absence
[3]candidate for degree only

Ennulat, Cynthia L., B.A. 1980, State University of New York, Oswego; M.S. 1985, Syracuse University. Major: Cell Biology and Genetics. Brewerton, New York

Escandon, Enrique M., B.S. 1983, M.S. 1985, Universidad Nacional Autonoma de Mexico. Major: Cell Biology and Genetics. Mexico City, Mexico

Evans, Elizabeth V., B.A. 1980, Bennington College. Major: Cell Biology and Genetics. La Jolla, California

Febbraio, Maria, B.S. 1982, Fordham University. Major: Microbiology, Immunology, and Pathology. Staten Island, New York

Fernandez-Almonacid, Rafael, B.Sc. 1980, M.Sc. 1985, Universidad Austral De Chile. Major: Molecular Biology. Valdivia, Chile

Firpo, Meri T., B.A. 1984, Carroll College. Major: Cell Biology and Genetics. Helena, Montana

Fotheringham, Robert Scott, B.Sc. 1985, University of Guelph. Major: Molecular Biology. Ontario, Canada

[2]Foxman, Brett, B.A. 1982, Boston University; M.D. 1982, Boston University School of Medicine. Major: Neurobiology and Behavior. Penn Valley, Pennsylvania

[3]Gamble, David A., D.V.M. 1978, Washington State University. Major: Microbiology, Immunology, and Pathology. Ithaca, New York

Geisberg, Mark S., B.S. 1985, Yale University. Major: Immunology. Leningrad, USSR

Gilbert, Gretchen E., B.A. 1982, Swarthmore College. Major: Molecular Biology. Syracuse, New York

Greenberg, Adam, A.B. 1981, Bard College. Major: Cell Biology and Genetics. New Rochelle, New York

Greenlee, Paul G., B.S. 1977, Oklahoma State University; D.V.M. 1980, Oklahoma State University; M.S. 1982, Oklahoma State University. Major: Microbiology, Immunology, and Pathology. New York, New York

Groden, Joanna L., B.A. 1978, Middlebury College. Major: Cell Biology and Genetics. Cambridge, Massachusetts

Gulati, Poonam, B.A. 1982, Cornell University. Major: Microbiology, Immunology, and Pathology. Collins, New York

[1]Gummere, Gregory R., B.A. 1979, M.S. 1981, University of Cincinnati. Major: Cell Biology and Genetics. Cincinnati, Ohio

Gundersen, Doris I., B.A. 1977, Clark University. Major: Cell Biology and Genetics. West Babylon, New York

Hahn, Mounou, B.S. 1985, University of Wisconsin. Major: Molecular Biology. Seoul, Korea

Hahn, Soonjung Lucia, B.S. 1983, Seoul National University; M.S. 1985, University of Wisconsin. Major: Molecular Biology. Seoul, Korea

Hearn, Timothy J., B.S. 1983, Penn State University. Major: Neurobiology and Behavior. Camp Hill, Pennsylvania

Heinrich, N. Julia, B.A. 1977, Brown University. Major: Molecular Biology. New York, New York

Hodgins, Gregory W. L., B.Sc. 1985, University of Toronto. Major: Molecular Biology. Ontario, Canada

Hong, Guangyuan, B.S. 1982, M.S. 1985, Peking University. Major: Molecular Biology. Peking, People's Republic of China

Huang, Chin-shiou, B.S. 1982, Kaohsiung Medical College; M.S. 1984, National Tsing Hua University. Hsinchu, Taiwan

Hume, Clifford R., B.A. 1983, Carleton College. Major: Immunology. Incline Village, Nevada

Hwang, Onyou, A.B. 1982. Smith College. Major: Neurobiology and Behavior. Seoul, Korea

Jenkins, Deborah L., B.A. 1983, Williams College. Major: Biochemistry. Amherst, Massachusetts

Johnson, Ellen L., B.A. 1983, Oberlin College. Major: Molecular Biology. Tarpon Springs, Florida

Kane, Eileen M., B.A. 1985, Hunter College. Major: Molecular Biology. New York, New York

Kanter, Madge R., B.A. 1982, University of California at Santa Cruz. Major: Molecular Biology. Palo Alto, California

Kelly, Catherine D., B.A. 1981, State University of New York at Purchase. Major: Microbiology, Immunology, and Pathology. Rockville Centre, New York

Kenny, Mark K., B.A. 1983, Wesleyan University. Major: Molecular Biology. Chappaqua, New York

Kim, Chul Geun, B.S. 1981, Han Yang University; M.S. 1983, Seoul National University. Major: Molecular Biology. Yesan, Korea

Knudsen, Beatrice S., M.S. 1982, University of Vienna. Major: Cell Biology and Genetics. Vienna, Austria

Kornack, David R., B.S. 1983, Northern Illinois University. Major: Neurobiology and Behavior. Lombard, Illinois

Künzi, Myriam S., B.A. 1984, Wellesley College. Major: Cell Biology and Genetics. Upper Malboro, Maryland

[1]Lader, Eric Scott, B.S. 1981, Brooklyn College. Major: Cell Biology and Genetics. Brooklyn, New York

Lee, Jin-Moo, B.A. 1985, Yale University. Fort Washington, Maryland

Lee, Myung Soo, M.D. 1979, M.M.S. 1980 Seoul National University (Korea). Major: Immunology. Dongdaemum-ku, Seoul, Korea

Leonard, Christopher, J., B.S. 1985, Cornell University. Major: Microbiology, Immunology, and Pathology. Rochester, New York

Li, Luyuan, Graduate Certificate 1982, Sichuan University. Major: Biochemistry. Zunyi City, People's Republic of China

Li, Mingxia, B.S. 1982, Beijing Second Medical College: M.S. 1985, Chinese Academy of Medical Sciences. Major: Pharmacology. Beijing, China

Lisanti, Michael, P., B.A. 1985, New York University. Major: Cell Biology and Genetics. Rockaway Beach, New York

Litherland, Sally A., B.S. 1981, University of Florida; M.S. 1983 University of Florida. Major: Microbiology, Immunology, and Pathology. Satellite Beach, Florida

Liu, Su, M.D. 1982, Shanghai First Medical College. Major: Molecular Biology. Hunan, China

Lu, Bai, B.S. 1982, East China Normal University; M.Sc. 1985, Shanghai First Medical College. Major: Neurobiology and Behavior. Shanghai, People's Republic of China

McDonald, William F, B.A. 1985, University of Florida. Major: Microbiology, Immunology, and Pathology. Jacksonville, Florida

McNerney, Mary Ellen, B.S. 1977, M.S. 1983, St. John's University. Major: Pharmacology. Huntington, New York

Maddock, Anne E., B.A. 1985, Yale University. Major: Physiology and Biophysics. Fairfield, Connecticut

Mahajan, Rohit, B.A. 1984, Swarthmore College. Major: Cell Biology and Genetics. Addis Ababa, Ethiopia

Maher, Kevin J., B.S. 1984, Manhattan College. Major: Microbiology, Immunology, and Pathology. Yonkers, New York

Maki, Robert G., B.A. 1985, Northwestern University. Major: Cell Biology and Genetics. Omaha, Nebraska

Mandell, James W., A.B. 1984, Cornell University. Major: Neurobiology and Behavior. Charlottesville, Virginia

Marino, Michael W., B.A. 1983, Skidmore College; M.S. 1985, University of Texas. Major: Cell Biology and Genetics. Racine, Wisconsin

[2]Martinez, Humberto Jose, M.D. 1975, University of Zulia Medical School (Venezuela). Major: Neurobiology and Behavior. Maracaibo, Venezuela

[1]Maurer, David H., A.B. 1977, Cornell University. Major: Immunology. Newburgh, New York

Meyers, Lillian R. S., A.B. 1984, Brown University. Major: Molecular Biology. Chicago, Illinois

Mok, Minsen, B.A. 1982, Johns Hopkins University. Major: Cell Biology and Genetics. Convent Station, New Jersey

Moncrieff, Patrice M., B.S. 1984, Boston College. Major: Cell Biology and Genetics. Park Ridge, New Jersey

Moran, Lorraine M., A.B. 1982, Mount Holyoke College; M.S. 1984, St. John's University. Major: Molecular Biology. New York, New York

Morham, Scott G., B.S. 1981, Hobart College; M.S. 1985, Texas A&M University. Major: Molecular Biology. Tarrytown, New York

Muench, Marcus O., A.S. 1983, College of Marin; B.S. 1986, University of California. Major: Cell Biology and Genetics. San Francisco, California

Murakami, Monica S., B.S. 1986, University of Maryland. Major: Cell Biology and Genetics. Yokohama, Japan

Nicholson, Andrew C., B.S. 1973, D.V.M. 1976, Michigan State University. Major: Microbiology, Immunology, and Pathology. Bangor, Maine

Nocka, Karl H., B.A. 1983, Bowdoin College. Major: Molecular Biology. Ridgewood, New Jersey

Norris, Carol Ann, B.S., B.A. 1981, Cabrini College; M.S. 1983, Villanova University. Major: Cell Biology and Genetics. Havertown, Pennsylvania

Nussenzveig, Daniel R., M.D. 1980, University of Sao Paulo. Major: Physiology and Biophysics. Sao Paulo, Brazil

O'Malley, Edward K., B.S. 1985, SUNY Stony Brook. Major: Neurobiology and Behavior. New York, New York

Parada, Camilo A., B.S. 1978, Licence Biology (Master of Science) 1981, Catholic University of Valparaiso (Chile). Major: Molecular Biology. White Plains, New York

Patil, Nila J., B.A. 1980, University of Buffalo. Major: Cell Biology and Genetics. Buffalo, New York

[2]Pearse, Roger N., B.A. 1977, Dartmouth College. Major: Microbiology, Immunology, and Pathology. Newport, Rhode Island

Pincus, David W., B.S. 1985, Yale University. Hampden, Massachusetts

Qiu, Feihua, M.D. 1979, Beijing Medical College. Major: Molecular Biology. Shanghai, People's Republic of China

Qiu, Wei-Qiao, M.D. 1982, Peking Medical College. Major: Immunology. Peking, People's Republic of China

Ramakrishna, Naren R., B.A. 1985, Johns Hopkins University. Charleston, West Virginia

Rempel, Rachel E., B.Sc. 1986, University of Toronto. Major: Cell Biology and Genetics. Oxford, England

Robertson, Donna A., B.S. 1979, Syracuse University. Major: Pharmacology. White Plains, New York

Romanski, Lizabeth M., B.A. 1985, Rutgers University. Major: Neurobiology and Behavior. Fort Worth, Texas

[2]Rosenberg, Charles D., A.B. 1978, Washington University; M.S. 1979, State University of New York at Buffalo. Major: Cell Biology and Genetics. Merrick, New York

Rosenberg, Elizabeth A., B.A. 1981, Wesleyan University. Major: Biochemistry. New York, New York

Rubino, Heidi M., B.S. 1980, Muhlenberg College. Major: Biochemistry. New York, New York

Russell, David S., B.A. 1982, Oberlin College. Major: Molecular Biology. Chagrin Falls, Ohio

Ryshke, Renee C., B.A. 1978, University of North Carolina. Major: Immunology. Long Branch, New Jersey

Sawyer, Douglas B., B.S. 1984, Cornell University. Major: Physiology and Biophysics. Beverly, Massachusetts

Sehgal, Amita, B.Sc. 1981, Delhi University (India); M.Sc. 1983, Jawaharial Nehru University School of Life Sciences (India); Major: Cell Biology and Genetics. New Delhi, India

Sgouros, George, B.S. 1984, Columbia University. Major: Physiology and Biophysics. Munich, Germany

Shaffer, Rose Mary, B.S. 1980, Loyola College. Major: Microbiology, Immunology, and Pathology. Baltimore, Maryland

Signorelli, Kathy L., B.A. 1982, Wellesley College. Major: Molecular Biology. Strongsville, Ohio

Solomon, David H., A.B. 1982, Oberlin College. Major: Molecular Biology. Montreal, Canada

[2]Sordillo, Emilia M., A.B. 1976, Harvard University; M.D. 1980, Cornell University. Major: Immunology. New York, New York

St. Angelo, Carol E., B.S. 1981, Mississippi University for Women. Major: Molecular Biology. Arlington, Texas

Steiner, Lisa E., B.S. 1985, Cornell University. Major: Developmental Therapy and Clinical Investigation. Batavia, New York

Stole, Einar, B.S. 1986, University of Washington. Major: Biochemistry. Seattle, Washington

Straub, Richard E., B.A. 1982, New College. Major: Cell Biology and Genetics. New York, New York

Strieter, Jon W., A.B. 1985, Princeton University. Major: Physiology and Biophysics. Brooklyn, New York

Studwell, Patricia S., B.S. 1984, State University of New York. Major: Microbiology, Immunology, and Pathology. Greenwich, Connecticut

Stukenberg, Peter Todd, B.S. 1986, Colgate University. Major: Molecular Biology. Syracuse, New York

Sullenger, Bruce A., B.S. 1986, Indiana University. Major: Molecular Biology. Centerville, Ohio

Szabó, Anikó, M.D. 1982, Szeged University Medical School. Major: Neurobiology and Behavior. Szeged, Hungary

Taddie, John A., B.S. 1986, Penn State University. Major: Molecular Biology. Indiana, Pennsylvania

Tan, Jimmy C., B.S. 1985, Ateneo de Manila University. Major: Molecular Biology. Manila, Philippines

Tantravahi, JogiRaju V., B.A. 1984, Columbia University. Major: Molecular Biology. Waltham, Massachusetts

*Teumer, Jeffrey K., B.A. 1979, Colgate University. Major: Molecular Biology. Sheboygan, Wisconsin

Thormodsson, Finnbogi R., B.Sc. 1980, University of Iceland. Major: Neurobiology and Behavior. Reykjavik, Iceland

Till, Martha L., B.S. 1975, Colorado State University. Major: Microbiology, Immunology, and Pathology. Chicago, Illinois

Tsukuda, Toyoko, A.A. 1975, Laney College; B.A. 1977, University of California. Major: Molecular Biology. Osaka, Japan

Tusie, M. Theresa, B.S. 1979, M.D. 1985, National University of Mexico. Major: Cell Biology and Genetics. Mexico City, Mexico

Underwood, Mark, B.A. 1981, University of Vermont. Major: Neurobiology and Behavior. St. Albans, Vermont

Vaughan, Kevin, B.A. 1984, Hamilton College; M.S. 1986, State University of New York at Buffalo. Major: Cell Biology and Genetics. Buffalo, New York

von Kreuter, Betsy F., B.S. 1982, University of Vermont. Major: Microbiology, Immunology, and Pathology. Darien, Connecticut

Walewski, Jose L., B.S. 1980, Pennsylvania State University; M.A. 1984, Boston University. Major: Pharmacology. Newton, Massachusetts

Weinstein, Catherine Ippolito, B.S. 1982, State University of New York at Stony Brook. Major: Biochemistry. East Meadow, New York

Winick, Jeffrey D., B.S. 1986, Worcester Polytechnic Institute. Major: Microbiology, Immunology, and Pathology. Boston, Massachusetts

Wong, Gwendolyn T., B.S. 1984, McMaster University (Canada). Major: Cell Biology and Genetics. Hamilton, Ontario, Canada

Wu, Kai-Yuan, B.A. 1983, New York University. Major: Molecular Biology. Shanghai, People's Republic of China

Yan, Hai, B.S. 1982, Nanjing University. Major: Biochemistry. Wuxi City, People's Republic of China

Yan, Ning, Diploma 1980, Nanjing University. Major: Biochemistry. Nanjing, People's Republic of China

Yokoyama, Midori, B.A. 1983, Pacific Lutheran University; M.S. 1985, Stanford University. Major: Neurobiology and Behavior. Tokyo, Japan

Zavitz, Kenton H., B.Sc. 1986, University of Toronto. Major: Molecular Biology. Niagara Falls, Canada

Zebala, John A., B.S. 1986, University of Southern California

Candidate for the Degree of Master of Science

Cuerdon, Elizabeth E., B.S. 1985, Siena College. Major: Microbiology, Immunology, and Pathology. Loudonville, New York

Entering Students

Abraham, Dicky G., M.S. 1987, Indian Institute of Technology. Major: Cell Biology and Genetics. Bombay, India

Bao, Luis V., B.S. 1987, Universidad Catholica (Chile). Major: Molecular Biology. Santiago, Chile

Bosenberg, Marcus, B.A. 1976, Cornell University. Middlesex, N.J.

Bradley, Roger S., B.A. 1984, Carroll College. Major: Cell Biology and Genetics. Laurel, Montana

Chu, Tang-Yuan, M.D. 1983, National Defense Medical Center. Major: Cell Biology and Genetics. Taipei, Taiwan, Republic of China

Claude, Alejandro, M.S. 1987, Universidad Catholica (Chile). Major: Molecular Biology. Santiago, Chile

Cupp, Judith A., B.S., B.A. 1987, Missouri Southern State College. Major: Immunology. Carl Junction, Missouri

Dakik, Habib A., B.S. 1985, American University of Beirut (Lebanon). Major: Neurobiology and Behavior. Beirut, Lebanon

de Bruin, Derik, B.S. 1986, Eastern New Mexico University. Major: Molecular Biology. Portales, New Mexico

Dratt, Sharon D., B.A. 1984, Sarah Lawrence College; M.S. 1987, University of Hawaii at Manoa. Major: Immunology. Honolulu, Hawaii

Erickson, David A., B.A. 1985, University of California at Santa Cruz. Major: Pharmacology. San Diego, California

Folger, Paula A., B.A. 1986, University of California at Santa Cruz. Major: Cell Biology and Genetics. Santa Cruz, California

Garepapaghi, Mohammed A., B.A. 1987, Bowdoin College of Maine. Major: Physiology and Biophysics. Orumieh, Iran.

Getts, Robert C., B.S. 1986, M.A. 1987, University of Scranton. Major: Biochemistry. Taylor, Pennsylvania

Gistrak, Michael A., B.A. 1985, Brown University. Westchester, New York

Glickstein, Lisa J., B.S. 1987, Cornell University. Major: Immunology. Apalachin, New York

Grün, Felix, B.A. 1987, Girton College, Cambridge University (England). Major: Immunology. Surrey, England

Hagler, Jeremiah, B.A. 1987, University of California at Santa Cruz. Major: Molecular Biology. Santa Cruz, California

Hawkins, Denise A., B.S. 1987, Scripps College. Major: Pharmacology. San Dimas, California

Huang, Hsien-Bin, B.S. 1984, M.S. 1986, National Taiwan Normal University (Taipei). Major: Biochemistry. Taipei, Taiwan, Republic of China

Lander, Harry, B.S. 1987, State University of New York at Stony Brook. Major: Biochemistry. Lido Beach, New York

Lim, Lorena C., B.S. 1979, University of the Philippines at Los Banos; M.S. 1987, University of South Carolina. Major: Molecular Biology. Laguna, Philippines

McAuliffe, Josephine M., B.S. 1987, Rochester Institute of Technology. Major: Molecular Biology. Poughkeepsie, New York

Mahmood, Umar, B.A. 1987, California Institute of Technology. Rockville, Maryland

Mayer, Alan, B.S. 1986, M.S. 12/1986, Emory University. Miami Beach, Florida

Miller, Mark, B.A. 1987, Brandeis University. Haverstraw, New York

Naftzger, Clarissa, B.A. 1985, University of California at Berkeley. Major: Immunology. La Jolla, California

Onel, Kenan, B.S. 1984, M.A. 1985, Yale University. Scarsdale, New York

Onrust, Rene, B.S. 1983, M.S. 1985, Auckland University (New Zealand). Christchurch, New Zealand

Przybylowski, Mark D., B.S. 1/1987, Rutgers University. Major: Molecular Biology. Middlesex, New York

Roberts, Gretchen D., B.S. 1976, George Washington University. Major: Cell Biology and Genetics. Brooklyn, New York

Roy, Nita, B.A. 1987, Hood College. Major: Molecular Biology. Bangalore, India

Rubin, Brian, B.S. 1984, M.A. 1985, Yale University. Scarsdale, New York

Schlemmer, Scott, B.S. 1987, Bowling Green State University. Major: Pharmacology. Stow, Ohio

Sebold, Joel H., B.A. 1984, M.A. 1985, State University of New York at Binghamton. Major: Radiation Physics (Master of Science Program). Brooklyn, New York

Seo, Yeon Soo, B.S. 1982, M.S. 1984, Seoul National University (Korea). Major: Molecular Biology. Seoul, Korea

Sherwood, Peter, B.S. 1985, Cornell University. Major: Molecular Biology. Ithaca, New York

Swarup, Rupendra, B.S. 1985, University of Maryland. Major: Molecular Biology. Rockville, Maryland

Tavorath, Ranjana, B.S. 1983, Hindu College of Delhi (India); M.B.B.S. 1983, Lady Haidinge Medical College of Delhi (India). Major: Molecular Biology. London, England

Treciokas, Amy B., B.A. 1987, Princeton University. Major: Immunology. Needham, Massachusetts

Xixis, George A., B.S. 1987, Massachusetts Institute of Technology. Major: Neurobiology and Behavior. Whitestone, New York

Yee, Nelson Shu-Sang, B.S. 1987, Massachusetts College of Pharmacy and Allied Health Sciences. Quincy, Massachusetts

Zhu, Yuan-Shan, B.A. 1978, M.D. 1982, Hunan Medical College. Major: Pharmacology. Changsha, People's Republic of China

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